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A Clinical and Histopathological Review of Autologous Chondrocyte Implantation in the Knee

Thesis submitted for the degree of Doctor of Medicine.

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MEMORANDUM

The work in this thesis is original. The collection of data, analysis of data and conclusions drawn are entirely the work of the author. Advice on statistical analysis was provided by Dr. Richard Morris and calculations made using SPSS software.

To avoid unintentional bias the histological specimens were prepared and assessed by Consultant Histopathologists who were blinded to what procedure the patient had undergone.

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Christopher Rees Gooding

Abstract

Osteochondral defects in the knee can be disabling causing persistent pain, giving way, locking, catching and swelling and a reduction in activities including sport. Traditionally symptomatic defects were treated with marrow stimulation techniques such as drilling, abrasion and microfracture of the subchondral bone which have had limited success with usually the production of a fibrocartilage repair. This repair tissue tends to be soft and degenerates over a period of time. Autologous chondrocyte implantation (ACI) has produced hyaline or hyaline-like repair tissue in experimental models and in the clinical setting in early studies, with the potential for permanent regeneration of articular cartilage, thus preventing early onset osteoarthritis.

This study reviews the clinical results of 3 techniques of autologous chondrocyte implantation (ACI): the more traditional periosteum covered ACI (ACI-P) implant, the collagen-covered ACI (ACI-C) and the matrix carried autologous chondrocyte implantation (MACI). Single cohort studies of ACI-P and ACI-C over a 4 year period were made together with the provisional results of the MACI procedure at 1 year. Then 2 prospectively randomized studies were performed to compare ACI-C with ACI-P and MACI with ACI-C. Finally a small series of patients were reviewed who had a chondrocyte implantation combined with other surgical techniques such as an anterior cruciate ligament reconstruction or tibial osteotomy.

A review of these patients revealed a significant improvement in their clinical scores over 4 years for the ACI-C and ACI-P technique in keeping with previously published data and also for the MACI technique at 1 year.

Interestingly, a large number of the ACI-P patients developed graft hypertrophy which required arthroscopic debridement since patients complained of pain and catching. However, the ACI-C and MACI patients rarely developed this problem. The prospectively randomised study did not show any difference in terms of clinical and histological assessment at 2 years between the ACI-C and ACI-P patients. The early results for the MACI technique are also comparable. Based on this data it is proposed that collagen-covered ACI is the present 'gold standard' in chondrocyte implantation rather than periosteum-covered ACI.

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I would also like to thank Professor Flanagan for her help in providing the photomicrographs of the histology specimens and also to Dr. Nan Mitchell at the Royal National Orthopaedic Hospital for explaining the magnetic resonance imaging of articular cartilage and its limitations!

I am also indebted to Johnson and Johnson for funding my Research Fellowship year and also to Claire Phillips and Kevin Edwards at Verigen (now Genzyme) for their administrative support.

Finally, this thesis is dedicated to my parents.

CHAPTER 1: INTRODUCTION
A REVIEW OF ARTICULAR CARTILAGE DEFECTS OF THE KNEE AND THEIR MANAGEMENT

The Problem with Articular Cartilage

Articular cartilage covers the ends of bones and by its structure and function, acts as a shock absorber as well as an extremely slippery surface for joint movement. It is essentially a type II collagen meshwork supported by water, which is held in place by the osmotic pressure of the proteoglycans produced by the chondrocytes (figure I). It is a tough, resilient substance, able to withstand very high levels of mechanical stress. But despite its toughness, it is susceptible to trauma and disease. If damaged, it loses its water content and degenerates. This may result in a spectrum of cartilage lesions varying from superficial lacerations to large defects extending down to the subchondral bone. A conservative estimate suggests 10,000 individuals damage their knee joint cartilage due to various injuries each year in the UK (Bentley 2000, Personal Communication).

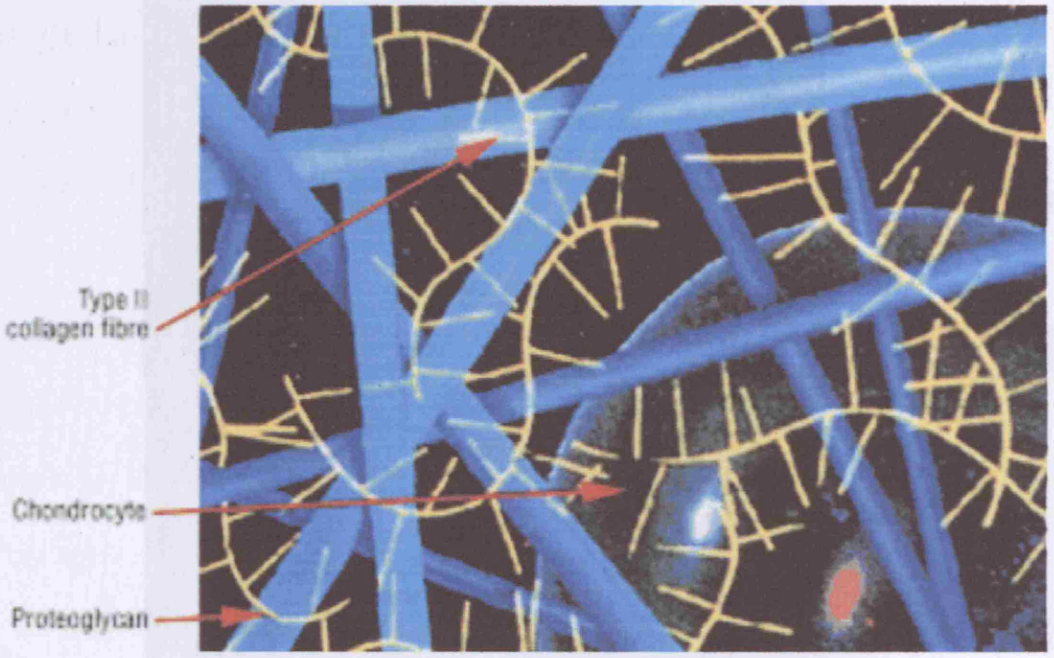

Figure I. Schematic representation of the spatial relations between collagen, proteoglycans and chondrocytes in cartilage (Courtesy of G. Bentley and BMJ [1])

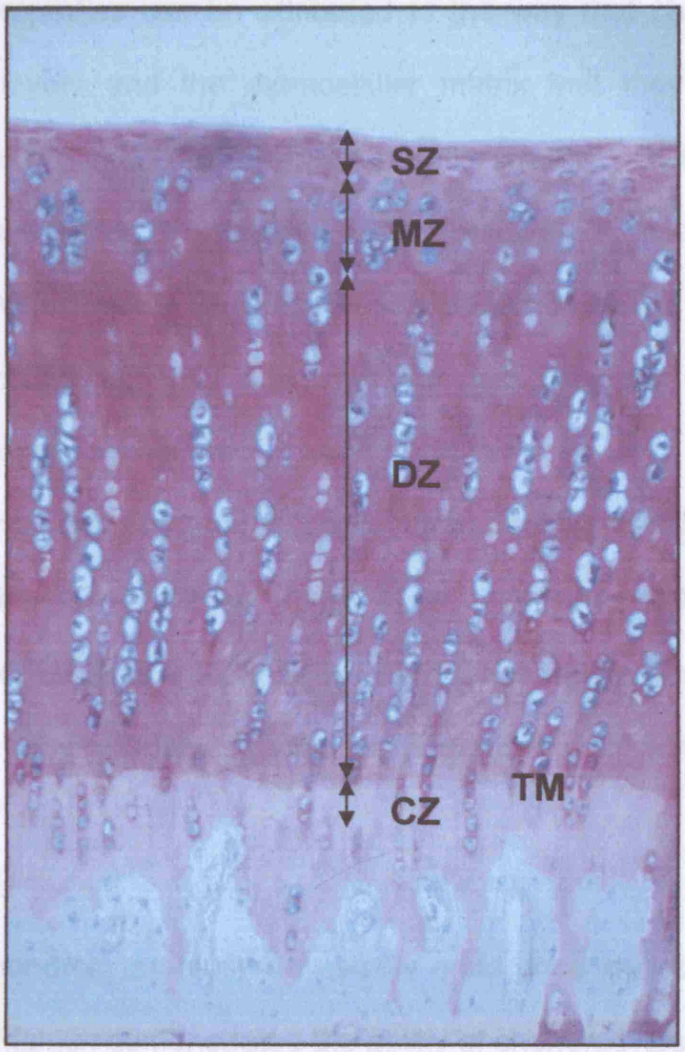

Figure II. Photomicrograph of normal articular cartilage showing the superficial (SZ), middle (MZ), deep (DZ) and calcified zones (CZ). The tidemark is also indicated (TM).

(Courtesy of G. Bentley)

Articular Cartilage Structure and Function

Articular cartilage possesses many unique characteristics, it provides a low friction surface allowing the smooth running of a joint and also enables it to transmit loads across and dissipate areas of high mechanical stress to the underlying bone.

These unique properties can be attributed to the way that chondrocytes are organized into layers and the extracellular matrix that they produce. The constituents that make up the extracellular matrix include collagen, proteoglycans and water, which envelop the relatively sparse population of chondrocytes. Water makes up 65-80% of the total weight of cartilage [4] the proteoglycans constitute 12% and chondrocytes 2%, and the remainder represents the collagen fibres [5].

It has been estimated that 90-95% of collagen in articular cartilage is type II [6]. The remaining 5-10% is made up of type V, VI, IX, X and XI. The structure of type II collagen constitutes a triple helix, which gives the cartilage its excellent tensile strength and robustness and provides the scaffolding of articular cartilage.

The ability of chondrocytes to divide usually ends once skeletal maturity has been achieved. Mankin demonstrated the ability of chondrocytes to divide in the skeletally immature. [7;8]. The almost complete inability of adult chondrocytes to divide and repair damaged articular surface is an important characteristic and is responsible for considerable morbidity.

Articular cartilage is one of a few tissues that does not possess nerve fibres so that injuries to its surface does not result in pain. It is only when the underlying bone is exposed that pain is felt.

Conventionally articular cartilage has been divided into layers or zones, the superficial, middle, deep and calcified (figure II). In the superficial zone the collagen fibrils are highly organised and have a preferential direction parallel to the articular surface; in the middle zone the fibrils have no real preferential direction and appear to have a random arrangement; and finally, the deep zone where fibrils are again highly organised and prefer a direction perpendicular to the subchondral bone. This is also known as the 'Benninghoff arcade model' [9]. The three dimensional structure of articular cartilage was demonstrated using the scanning electron microscope by Jeffrey et al in 1991(figure III) [3]. This revealed that in the middle and superficial zones there is a series of closely packed layers or leaves. Each of the leaves is composed of a fine meshwork of collagen fibrils and are bound to other leaves by bridging fibrils. In the calcified and deep zone, the fibrils are arranged in vertical bundles and are also bound to each other with fibrils. The leaves formed in the middle zone then arch over to form the horizontally orientated leaves of the superficial zone. A similar close association between the horizontal leaves exists with numerous bridging/interconnecting fibrils.

As well as differences in its three-dimensional structure, each zone possesses many other distinctive characteristics. Cells found in the superficial zone are characteristically flattened due to the shearing forces that they are exposed to and secrete a lubricant called lubricin. Lubricin is a glycoprotein found in synovial fluid and prevents direct surface to surface contact at an articulation. The thickness of this layer varies between 1 and 100 nm. Lubricin is secreted by other cells such as the synovial lining cells and enables the smooth running of the joint as well as preventing wear. The synovium also secretes hyaluronic acid, proteinases, collagenases and prostaglandins. These constituents are

added to an ultrafiltrate of blood plasma, which together make up the synovial fluid. As well as lubricating the joint, the synovial fluid also provides nourishment for the articular cartilage.

Cells in the superficial zone secrete an extracellular matrix containing a large aggregating proteoglycan (aggrecan), similar to cells found in other zones. This molecule is able to bind large amounts of water and is responsible for the resilience of cartilage to compressive forces. Cells in the superficial zone are exposed to the greatest shearing forces and it is here that the greatest concentrations of collagen fibrils are found [10]. Infact their ability to resist compressive forces is of less importance, which is why this zone possesses the lowest concentration of aggrecan.

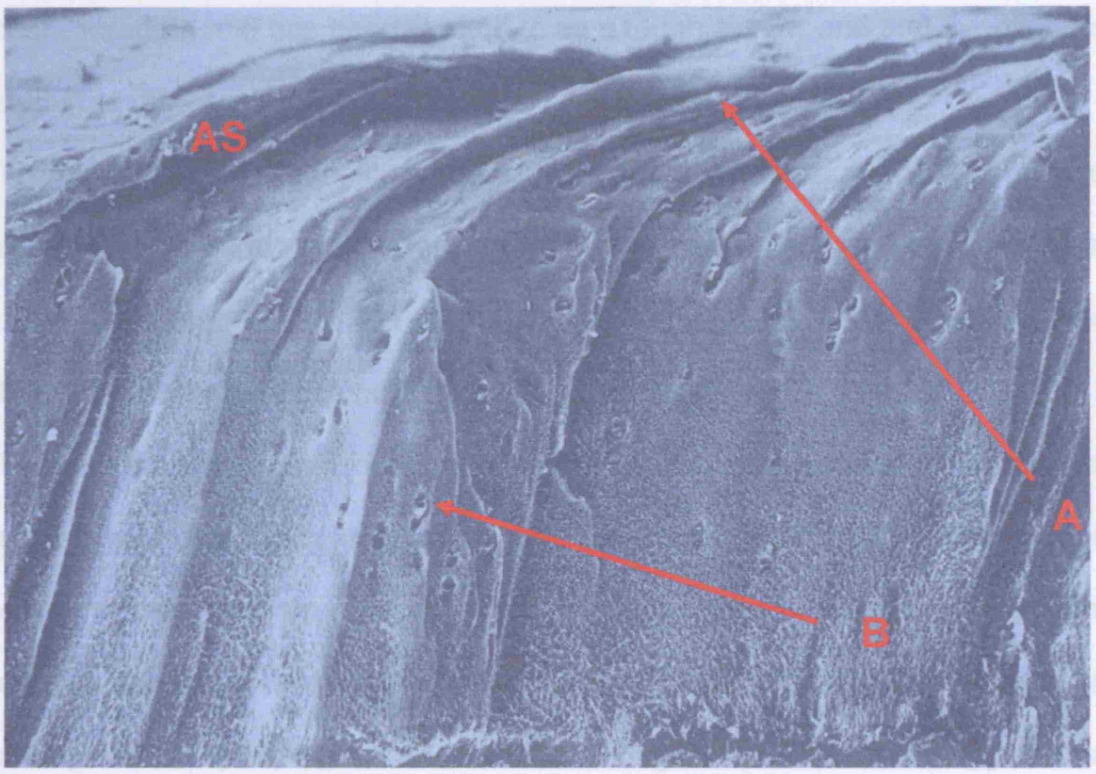

Figure III. Electron micrograph of articular cartilage after freeze fracturing, demonstrating the collagen leaves (A) which curve over in the middle zone to lie in the horizontal plane, parallel to the articular surface (AS) in the superficial zone. (B) indicates the isolated chondrocyte lacunae within the leaves [3]. (Courtesy of the British Journal of Bone and Joint Surgery).

Type II Collagen fibrils in the superficial zone are narrower than those found in the deeper zones (diameter 20 nm compared with > 100 nm) and are arranged parallel to the surface of the cartilage to a depth of 50 – 100μm [11]. The comparatively low concentration of aggrecan and the parallel arrangement of numerous narrow collagen fibrils in the superficial zone contribute to its high tensile strength and has been likened to as a tough skin or rind that overlies the rest of the cartilage.

The middle zone (or transitional zone) is thicker than the superficial zone and contains more rounded chondrocytes with wider type II collagen fibrils that lie in a random arrangement. The matrix found in this zone, which envelops the fibrils, also contains a higher concentration of aggrecans.

The deep zone (or radial zone) contains the highest concentration of aggrecans and it is here that the collagen fibrils with the greatest diameter are found. The collagen fibres are arranged in a parallel fashion perpendicular to the joint surface. The middle and deep zones are largely responsible for the resilience of cartilage to compressive forces due to the large concentration of aggrecans, but provide little resistance to shearing forces due to the low concentration of collagen fibrils unlike the superficial zone.

Chondrocytes of the deep zone are characterized by being spheroidal in shape and arranged in a columnar orientation. This zone is also unique in that it is part calcified and becomes the calcified zone. The tidemark is a calcification front where non-calcified cartilage meets calcified cartilage. Chondrocytes found in the calcified zone are able to calcify their extracellular matrix and are rich in alkaline phosphatase. The collagen fibrils are inserted into the calcified cartilage ensuring that it is securely anchored to the underlying subchondral

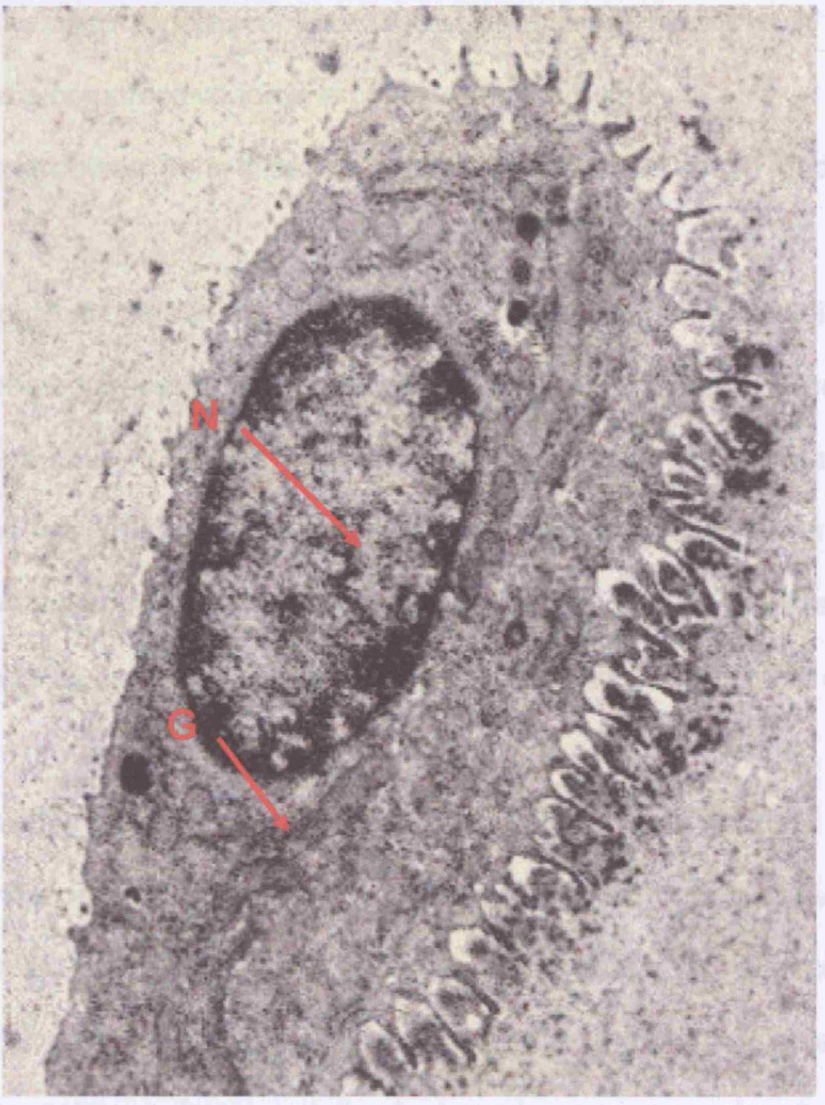

Figure IV. Electron micrograph of a chondrocyte in its lacuna. Some of the organelles can be seen clearly in this picture including the nucleus (N) and the Golgi apparatus (G). (Courtesy of J.A. McNulty, Loyola University Chicago Stritch School of Medicine).

bone. As cartilage degenerates as seen in osteoarthritis the calcified zone may progress further into the deep zone. This may result in two tidemarks being seen. The more superficial tidemark represents the extension of the zone of calcification and the deeper one being the original tidemark [11]. Clearly, if the matrix of the deep zone becomes calcified its ability to 'spring back' after being exposed to a compressive force is considerably reduced.

Thus, chondrocytes from different zones differ in size, shape and metabolic activity.

The proteoglycan monomers (aggrecans) consist of a central protein core with many sulphated gylcoaminoglycans (GAG's) bound to it (figure V and VI). The GAG chains have numerous negative charges and are therefore able to bind cations and are hydrophilic. As a result the glycoaminoglycan chains are able to bind water molecules tightly within cartilage. This is a key characteristic of gylcoaminoglycans and is responsible for the robust structure of articular cartilage.

Also by having numerous side chains with negative charges, they repel each other, so the proteoglycan aggregates tend to spread out. In native cartilage aggrecans are only partially hydrated due to the compressive forces that are exerted on them by the collagen framework made up of type II collagen fibrils. Thus if the collagen framework is destroyed, aggrecans absorb water and expand (as seen in chondromalacia patellae) and early osteoarthritis.

Articular cartilage can be viewed as a type of sponge, although considerably more resilient due to its integrity being maintained by the strong hold that the aggrecans have for water and the collagen framework which holds it altogether under tension.

As well as the differences mentioned above between each zone, there is also considerable variability within each zone. Surrounding each chondrocyte there is relatively little collagen but high concentrations of aggrecans (pericellular matrix). Enveloping this region, surrounding the cells and the pericellular matrix there is a web of thin collagen fibrils, which may provide some protection for the cells (territorial matrix). The area found between the territorial matrixes is called the interterritorial matrix. Here, the organisation of the cartilage is dictated by its mechanical function, and the collagen fibrils are arranged as previously described for the various zones.

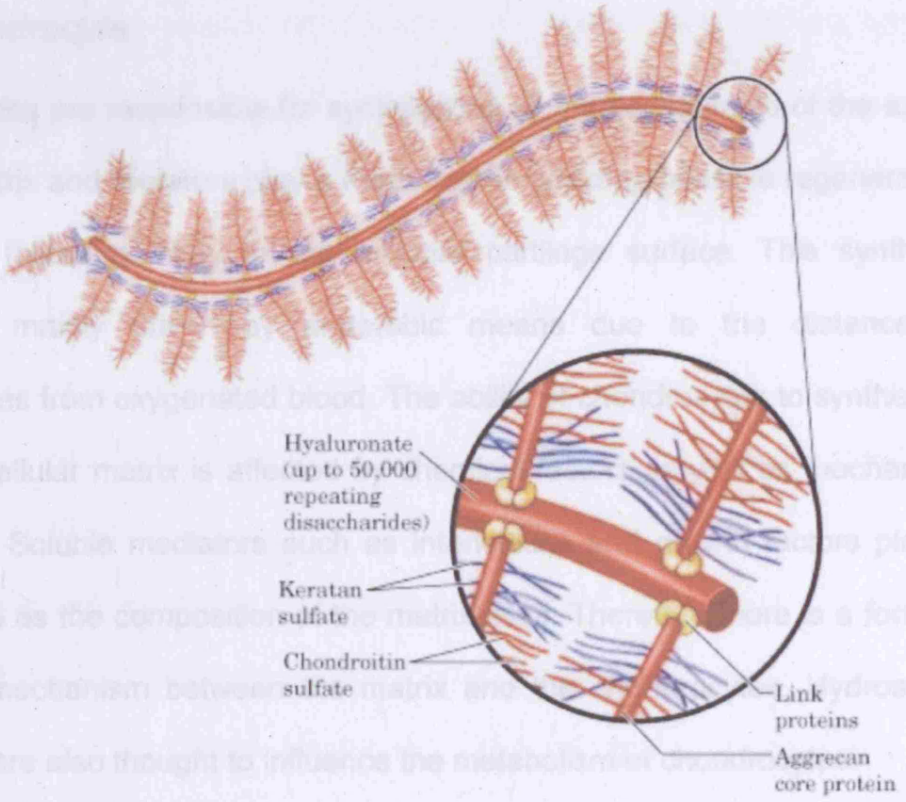

Figure V. A schematic diagram demonstrating the structure of aggrecans. Each monomer consists of a central protein core with many sulphated glycoaminoglycans (e.g. Keratan sulphate and chondroitin sulphate) bound to it. (Courtesy of the University of Texas).

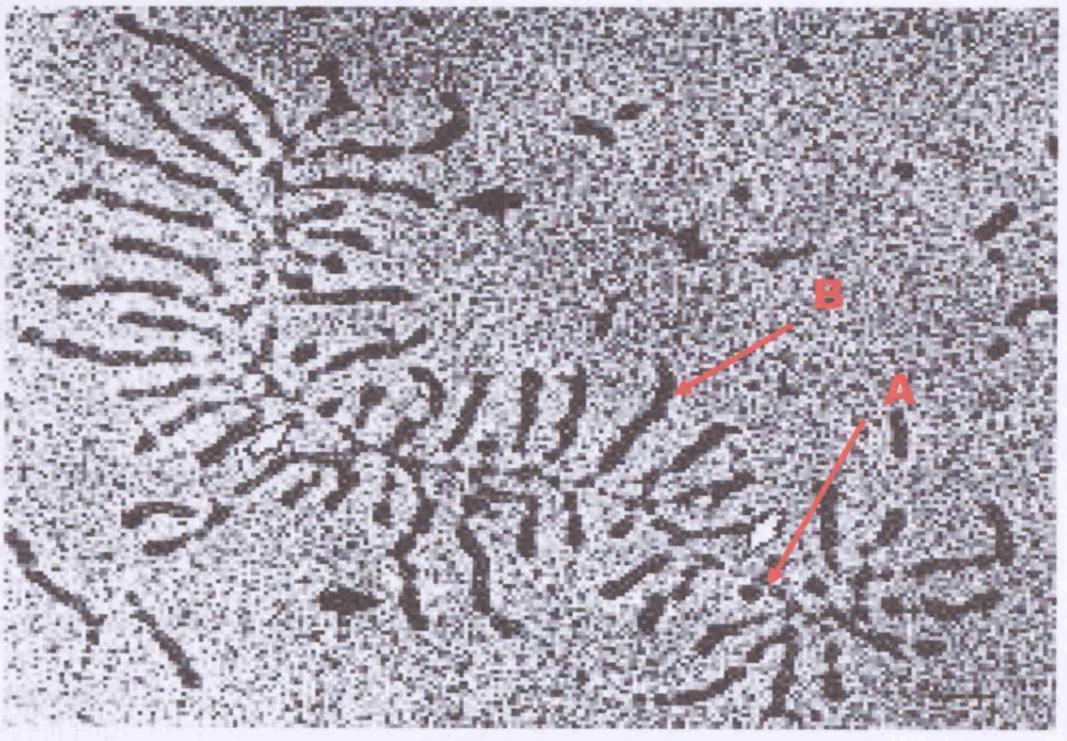

Figure VI. An electron micrograph showing the structure of an aggrecan. Branching off hyaluronate (A) are many core proteins (B) with numerous sulphated glycoaminoglycans attached (Courtesy of the University of Kuopio).

The Chondrocyte

Chondrocytes are responsible for synthesizing all the constituents of the extra-cellular matrix and therefore play a major role in directing possible regenerating processes following injury to the articular cartilage surface. This synthetic activity is mainly driven by anaerobic means due to the distance of chondrocytes from oxygenated blood. The ability of chondrocytes to synthesize the extra-cellular matrix is affected by chemical factors as well as mechanical influences. Soluble mediators such as interleukins and growth factors play a role as well as the composition of the matrix itself. Therefore there is a form of feedback mechanism between the matrix and the chondrocytes. Hydrostatic pressures are also thought to influence the metabolism of chondrocytes.

In the osteoarthritic patient there is evidence to suggest that chondrocytes are able to synthesize new matrix but many of these molecules are degraded by proteolysis [11;12].

In the young growing child, damage to the articular cartilage also stimulates the synthesis of new type II collagen fibres as well as proteoglycan.These new fibres are not destroyed by proteolysis and may account for the fact that symptoms can resolve following an injury in a growing child. Hence considerable work has been done to investigate possible antagonists to the proteolytic agents that occur in osteoarthritis. Some success has been seen with antagonists to Interleukin-1 (IL-1) and tumour necrosis factor-α which are known to suppress type II collagen and aggrecan synthesis (Kobayashi, M. et al: unpublished data). There may be further scope for this therapeutic option in future research.

Another important characteristic of articular cartilage in the young is that chondrocytes are able to proliferate, however once skeletal maturity is reached

the cells rarely divide under normal conditions although cell division is seen in osteoarthritis [13].

The fact that cartilage is relatively acellular means that its ability to repair itself is impeded and as cartilage ages the number of cells reduces due to apoptosis, further impairing its ability to synthesize new matrix.

The interplay between chondrocytes and the extracellular matrix they produce together with their arrangement into zones explains the unique characteristics of articular cartilage.

These unique characteristics together with the inability of articular cartilage to repair itself have posed a significant clinical problem for many years. The observation made by William Hunter is just as relevant today as it was 260 years ago and it strikes at the core of the problem of the management of osteochondral defects.

'From Hippocrates down to the present age, we shall find, that an ulcerated cartilage is universally allowed to be a very troublesome disease; that it admits of a cure with more difficulty than a carious bone; and that, when destroyed, it is never recovered'

W. Hunter 1743 [14]

Repair of Articular Cartilage

Full thickness articular cartilage defects are never restored to normal cartilage by natural methods [15]. Damaged articular cartilage may repair itself with fibrocartilage, but this requires vascular in-growth from the subchondral bone. Fibrocartilage may restore the joint surface to a functional level, but often this

result is 'short-lived' since it is less resilient than hyaline cartilage so that continued trauma to the articular surface eventually leads to its degeneration [16]. This is due to the relative preponderance of type I and III and the absence of type II collagen. Even so there are several treatment methods currently used that encourage vascular in-growth and subsequent repair by fibrocartilage formation for which good clinical results are claimed [17-33].

The poor ability of articular cartilage to regenerate, contrasts with bone, which has an excellent ability to regenerate despite the fact that both cartilage and bone share the same progenitor cells. So why can bone regenerate and cartilage cannot?

Caplan et al [34] in their review of cartilage repair and regeneration address this issue. The key to bone healing is the arrival of numerous progenitor cells to the fracture site. These progenitor cells and other repair cells together form a blastema which goes on to form a callus and then through a process of remodelling forms new bone over the old fracture site. Unlike bone, cartilage has no blood supply of its own, so progenitor cells and other repair cells are unable to migrate to the site of damage.

Avascularity may be one factor that is responsible for the inability of cartilage to heal, also the immobility of the chondrocytes trapped in the extracellular matrix and the limited ability of mature chondrocytes to divide and increase their synthetic activity, also plays a role [35]. Hence a logical way to repair such defects with hyaline cartilage is to artificially deliver chondrocytes to the site of injury where they may form new matrix. The first reported case of a repair of an osteochondral defect in a human subject by the siting of cultured autologous chondrocytes underneath a periosteum cover was reported in 1984 by Brittberg et al [36] in Sweden.

Aetiology of cartilage defects

For the purposes of this review, the aetiology of the various defects has been classified into those of traumatic origin, those attributed to osteochondritis dissecans and those due to chondromalacia patellae.

Traumatic Cartilage Defects

By far the largest group are those patients whose defects are of traumatic origin and are commonly found on the medial femoral condyle.

Knee trauma is common in high performance athletes such as soccer players, reportedly accounting for 20% of all their injuries [37]. This high incidence maybe explained by the high velocities and repetitive high impact twisting movements that occur within the knee when kicking a soccer ball or by contact injuries placing extreme stresses on the articular cartilage [37].

Traumatic chondral injuries are believed to occur through two distinct mechanisms. The largest group arises through abrasive wear, which results in superficial fibrillation. Often at this stage the lesion is asymptomatic until erosion progresses to the subchondral bone.

The second type of lesion occurs because of disruption to the deep cartilage ultra-structure by large shear forces. Ateshian [38] demonstrated that shear stress is concentrated at the junction of the uncalcified and calcified cartilage, which may produce damage to the cartilage above the tidemark but also to the subchondral bone. Levy et al [37] confirmed this when they performed biopsies of the base of osteochondral defects in soccer players at the delamination border revealing that the calcified cartilage remained with the subchondral bone.

Osteochondritis Dissecans

Osteochondritis dissecans is a localized disease and involves the separation of a fragment of the subchondral bone and overlying cartilage (hence dissecans). It is found most commonly in the ankle, elbow and knee. However the knee is the most frequent site, affecting 75% of patients [39]. From the name it could be assumed that an inflammatory process is responsible for the development of such a condition ,however, Nagura in 1960 demonstrated the absence of inflammatory cells in histological sections of excised osteochondral fragments [40]. None the less, the name osteochondritis endures. As well as a possible inflammatory process other aetiologies have been suggested such as indirect trauma [41 42], ischaemia [43;44] as well as defects of ossification [45;46] and genetic causes [46;47]. However, to this day little is known about how this disease process develops and it has been surmised that the factors responsible vary according to the specific joint involved and on the specific site within the joint [48].

The condition has been subdivided into the juvenile and adult form. Children and adolescents between the ages of five years and fifteen years who still have open physes have the juvenile form [49]. Older children with closed physes and adults, have the adult form. The condition is rare in those aged 10 years or less and those more than 50 years old [50]. It had been suggested that although adult osteochondritis may arise de novo, it is more likely that such patients initially had an asymptomatic juvenile osteochondritis dissecans, which failed to heal and later developed into a symptomatic defect [48].

Patients with osteochondritis dissecans often present in a fashion similar to those with traumatic defects. Patients may complain of pain, swelling, locking and giving way. Often the symptoms are intermittent and are related to the level

of activity of the patient. If there is a cartilaginous or osteochondral loose body present, the symptoms may be more constant with locking, pain and swelling. The lesion commonly affects the weight-bearing area of the lateral aspect of the medial femoral condyle [42]. However, it can affect both weight bearing and non-weight bearing areas of the joint [51].

Children with open growth plates have the best prognosis and are best treated with conservative management. Schenck and Goodnight [48] concluded on the basis of their review of the literature that children with symptomatic lesions should be managed initially with reduction in activities until they no longer have symptoms. They advocated protected weight-bearing to allow healing of the subchondral bone and to prevent further damage. Clearly it can be difficult to limit the activities of a child so they suggested using a knee immobiliser or a splint. These patients should be carefully followed up in the orthopaedic clinic with regular clinical examinations and serial radiographs and possibly serial MRI's. They advocated operative treatment only if there are loose bodies present, or if symptoms persist for 6-12 months, or if healing is deemed unlikely based on observations of the radiographs that show fragments that are completely separated from the articular surface and are displaced. Children who are symptomatic despite a trial of non-operative treatment and who are approaching skeletal maturity may be considered for operative management.

Older patients often become symptomatic and without treatment may progress to osteoarthritis. There are various treatments available for this patient group such as curettage and drilling of the base of the defect or chondrocyte transplantation.

This line of management is supported by Linden's work that described the natural history of osteochondritis dissecans in fifty-eight patients with a mean

follow up of 33 years. He observed that children with open physes with defects attributed to osteochondritis dissecans did not go on to develop secondary degenerative changes, however 38 of 48 patients who had first developed the condition after closure of the physes had progressed [52]. The treatment of osteochondritis dissecans continues to be a controversial subject and the aetiology remains unclear. However, in treating this condition it is important to differentiate between the juvenile form of the condition and the adult form.

Chondromalacia Patellae

Chondromalacia patellae or softening of the articular cartilage of the patella is a common finding at arthroscopy and is most commonly found in patients aged 15 to 35 years [53]. Normal healthy articular cartilage is bluish-white, smooth, glistening and resilient. With chondromalacia patellae the earliest change is that the cartilage becomes a dull, yellowish-white and is soft and swollen [54]. Usually this area of abnormal cartilage is found in the medial patellar facet on the most medial or 'odd' facet [55] and is approximately 1 – 2 cm in diameter. With time, irregular fissures develop and the area becomes a mass of frond–like material attached to the subchondral bone. The affected area tends to increase in size and its centre becomes eroded down to the underlying subchondral bone. As the size of the affected area gets bigger the lateral facet may become incorporated into the defect so that the whole retropatellar surface may be involved but in 30-50% of individuals the condition appears not to progress.

There have been many theories of the aetiology of chondromalacia patellae in the past, including a direct or indirect injury to the patella or a generalised constitutional problem. At present the most likely cause is thought to be due to chronic or recurrent overload of the retropatellar surface. This may be due to the fact that the patella and femoral joint surfaces are not congruent or to

abnormal tracking of the patella during flexion and extension. However, Dowd and Bentley [56] showed that chondromalacia could occur without any joint instability suggesting that in some cases it may be genetic. Chondromalacia patellae is very common; Outerbridge observed in 196 cases of medial menisectomy that 101 patients showed evidence of the condition [54]. This pathological state can be associated with retropatellar pain and other symptoms including joint swelling and giving way, this can lead to considerable disability with associated restrictions of activity [53].

However not all patients are symptomatic, explaining the relatively high incidence at arthroscopy and low numbers of patients presenting with the condition in the Orthopaedic Clinic[57]. Also, approximately 50 percent become asymptomatic with time which could indicate spontaneous healing of the cartilage[58]. None the less there remains the concern that patients with symptomatic chondromalacia patellae may go on to develop osteoarthritis, although at present there is little in the literature to support this.

Response to injury in connective tissue

The avascular nature of articular cartilage poses a significant problem in its response to injury [59]. The response of the majority of organs to trauma usually follows a similar path. This sequence of events can be divided into 3 distinct phases: necrosis, inflammation and repair [59].

Necrosis is set in motion as soon as the injury occurs. The extent of this phase is dependent on a number of factors including the type and severity of trauma and the vascular supply. The vascular supply is important for three reasons. Different organs have varying sensitivities to the interruption of their local blood supply. The heart and brain are extremely sensitive to any interruptions of their

blood supply whereas skin is more resilient. Also some organs have a far richer blood supply than others and some have the potential to open up a rich collateral circulation. Therefore tissues that are subjected to a severe injury, with a poor vascular supply, with little ability to open up a collateral circulation and are made up of cells that are extremely sensitive to ischaemia undergo extensive necrosis.

Following necrosis there is a phase of inflammation. In this phase the vascularity of the organ again plays an important part. Blood vessels are able to dilate resulting in increased blood flow to the injured tissue. When the vessels dilate the pore size between the endothelial cells which make up the capillary walls enlarge, and as a result, become more permeable allowing the migration of cells from the capillary lumen to the extracellular space. Fibrinogen also leaks out and following an enzyme driven cascade forms a fibrin meshwork, which also contains numerous inflammatory cells that mop up any cell debris. Towards the end of this phase the fibrin meshwork becomes organised and forms a scaffold and the next phase then commences.

The third and final phase is often the longest phase. The repair phase starts with the neovascularisation of the fibrin scaffolding that was formed during the inflammatory phase. The newly formed vascular supply conducts cells to the site of injury that are needed for repair. Fibroblasts found within the fibrin meshwork lay down a fibrous matrix that later develops into a scar. Rather than repairing the site of injury with scar tissue some tissues are able to replace like with like. For example with a fracture, bone is able to repair itself with new bone and in the case of the liver it is able to regenerate itself. Clearly with articular cartilage repair the response is impaired by the avascular nature of cartilage.

During the first phase of healing, the extent of necrosis is less than one may expect compared with other organs.

Being part of an avascular structure chondrocytes are relatively insensitive to hypoxia resulting in less necrosis following trauma. The inflammatory phase is non-existent in the healing of articular cartilage since there are no blood vessels. This has considerable implications for the final phase, since there are no vessels to conduct cells to the site of injury that are needed for repair. Hence a superficial injury that significantly disrupts the chondrocytes and extracellular matrix but does not breach the subchondral bone has very little capacity to heal [60]. The only possibility for repair in superficial lesions is from the chondrocytes near the edges of the defect which undergo transient proliferation [61].

Although the above description is true for superficial injuries to articular cartilage, deep injuries that involve the subchondral bone follow a different course. Subchondral bone is perfused with numerous blood vessels and if this area is involved in the injury then the inflammatory phase of healing is able to play a role.

For the purpose of this review a deep injury is considered as a defect that breaches the tidemark and penetrates the subchondral bone. Such an injury will precipitate bleeding and the formation of a haematoma, which subsequently becomes organised into a fibrin clot. Cells trapped within the fibrin clot include undifferentiated cells from the marrow and endothelium and white blood cells, which differentiate into primitive fibroblasts. Together with the ingrowth of new capillaries from the subchondral bone, the fibrin clot ultimately becomes granulation tissue. Meanwhile, at the base of the lesion new bone forms and grows towards the joint. The new bone formation only continues until it fills the

bony defect and stops at the boundary between the calcified cartilage and subchondral bone. Therefore at this stage the deep part of the defect is restored with new bone and the cartilage part of the defect is filled with granulation tissue. The granulation tissue is fused to the underlying new bone and unites with the adjacent cartilage found at the rim of the defect.

Chondrocytes found at the rim of the defect undergo a minimal response to the injury similar to what occurs following a superficial lesion. Meanwhile the granulation tissue residing within the defect becomes gradually replaced by fibrocartilage which contains type I and type III collagen mainly.

However, research by Salter et al in 1980 [62] showed that continuous passive motion appeared to influence the healing of cartilage following a deep laceration. Their results showed that by subjecting the injured joint to continuous motion the defect healed more rapidly and the repair tissue had features of hyaline cartilage rather than fibrocartilage.

Mankin concluded from his review of the literature that superficial lesions undergo minimal healing but deep lacerations that penetrate the bone stimulates a full blown healing response and may result in a mixed hyaline / fibrocartilage repair. He also suggested that depending on the size of the defect that such an injury may lead to a focus for osteoarthritis [63]. Further reviews have suggested that repetitive loading injuries to the cartilaginous surface that exceed a certain threshold may result in damage to the chondrocytes and underlying bone leading to features of osteoarthritis [64].

The Natural history of Osteochondral defects

Full thickness chondral injuries secondary to work related and sporting activities are common with an incidence of between 5%-10% of acute haemarthrosis [4].

Despite this high incidence very little is known of the natural history of osteochondral defects, which poses a difficult problem of when to treat such injuries.

Animal models have been used to explore the natural history of osteochondral defects however their cartilage often possesses different properties from those of human cartilage and the lesions created rarely resemble those seen in human knees.

Messner and Maletius performed a study of a population of 28 young athletes who had previously been diagnosed with severe isolated chondral damage in the weight-bearing areas of their knees [65]. They noted that at 14 years, only 7 patients still performed at their pre-injury activity level. The remaining 21 patients showed a reduction in activities during the follow-up period. These patients also had knee radiographs repeated at 14 years which showed that 12 patients had no radiographic signs of arthrosis in the injured knee, 4 patients had Grade 1 arthrosis, 11 had grade 2 and 1 patient had Grade 3. This suggested that along with a clinical deterioration there was a permanent deterioration seen on the knee radiographs following a cartilage injury.

Curl et al concluded from their review of 31,516 arthroscopies where 19,827 or 63% had chondral lesions, that 'significantly injured articular cartilage is never spontaneously restored to normal articular cartilage' [15].

Hernborg and Nilsson described the course of events in untreated knee arthrosis [66]. This study was based on non-weight bearing radiographs of knees taken at the time of presentation 10 to 18 years earlier. At subsequent follow-up a clinical examination was made and weight-bearing radiographs were taken which showed that greater than half had deteriorated both clinically and radiographically.

Similar research by Spector et al, found that 33% of their patients deteriorated during an average of 11 years [67].

A number of factors have been found which exacerbate this deterioration. Such factors include obesity, meniscal tears, sport activities and certain occupations. Also, there has been shown to be an increasing prevalence with age [68].

Sahlstrom and colleagues [69] looked for joint space narrowing on weight bearing radiographs of the knee in their review of patients with knee arthrosis. They observed that 70% of knees with Ahlback Grade 1 or higher, deteriorate over a 20 year period (Ahlback Grade 1: sharpening of the edges, the beginning of osteophytes, sclerosis and flattening of the condyles and joint space narrowing up to 50% [70]).

In the case of the natural history of osteochondritis dissecans, patients with juvenile osteochondritis frequently heal. However, those lesions that do not heal and continue after closure of the physes rarely heal with non-operative management [51]. It has been hypothesized that in both the juvenile and adult forms of osteochondritis dissecans that the articular cartilage softens as it loses its anchorage to the subchondral bone. If the disease process is allowed to proceed unhindered, some minor trauma may then knock off an osteochondral fragment resulting in a crater in the articular surface and a loose body in the joint. With separation of the fragment from the underlying bone, healing becomes unlikely. If the lesion involves a weight bearing surface, the incongruity of the articular surface predisposes the joint to more advanced changes as seen with degenerative joint disease.

There is still much to discover about the natural history of osteochondral defects from whatever cause and the majority of studies document the

deterioration of early osteoarthritis rather than discrete osteochondral defects as can be seen from the above. A large number of isolated chondral injuries are discovered incidentally at arthroscopy although not all patients complain of pain as their main symptom. Although there are techniques available that can restore the articular surface, surgical intervention may not always be indicated. From a review of the literature the best guide for the management of osteochondral defects is the Surgeons' best judgment in ascertaining that the patient's symptoms are explained by the presence of the defect. Once the surgeon is confident that the defect is responsible for their symptoms then surgical intervention is probably indicated.

Diagnosing articular cartilage defects

Clinical Assessment

The management of any clinical problem always starts with the history and examination.

Pain is the most common presenting complaint of a patient who has sustained an articular cartilage injury. Ochi et al [71] and Brittberg et al [36] have reported symptoms such as locking, pain, swelling and retropatellar crepitus. Peterson et al [72] described them as severe symptoms with pain at rest. Hangody et al [73] defined them as pain, pain with activity, swelling and locking.

In Levy et al's [37] study of chondral delamination of the knee in soccer players, patellar and trochlear lesions were associated with reports of pain during jumping, deceleration and the extension phase of kicking. Anterior condylar lesions produced pain during the extension phase of kicking. Central condylar lesions produced pain during pivoting and lateral movements. Posterior

condylar lesions were painful during the flexion phase of kicking and during planting of the non-kicking leg to the ground.

Often patients report that the affected knee gives way when walking or when going down stairs. On further questioning these patients often recall that immediately preceding the knee giving way they notice an intense sharp pain from within the knee.

This episode of intense pain may coincide with the osteochondral defect coming into contact with the opposing joint surface during the weight-bearing phase of walking. The giving-way is therefore a response to the intense pain. Giving-way may also occur independent of pain. In this situation the instability maybe explained by the presence of quadriceps wasting or an anterior cruciate ligament (ACL) rupture.

Occasionally the patients may complain of locking similar to the presenting complaint of a meniscal tear. In the case of an osteochondral defect being the cause, this may be attributed to an osteochondral fragment that has broken off from the joint surface impairing the smooth running of the knee.

The patient should have a thorough examination of gait, alignment of the lower limbs and evidence of generalised joint laxity should be sought. One should look for the presence of an effusion and evidence of joint instability due to ligament damage and patello-femoral maltracking.

Localised bone or joint line tenderness maybe the only positive finding found on examination. Some authors have reported as high as a 94% incidence of a specific mechanism of injury and joint line tenderness with chondral lesions in mixed populations and an 83% incidence of an effusion, although others have noted no correlation between clinical signs and articular cartilage damage [74;75].

Clearly a finding of joint line tenderness may also be found with other knee pathologies such as a meniscal tear.

The examination findings together with information obtained from the history may suggest the presence of an osteochondral defect. This can be confirmed with the use of imaging and arthroscopy.

Investigations

There are a number of investigations that are used to assess the presence of an osteochondral defect and exclude other pathologies. Often large defects show up on a plain radiograph (figure VII), smaller defects may be detected on an MRI scan (figure VIII).

Plain Radiographs

Weight-bearing anteroposterior (AP) ideally full length and lateral radiographs of the knee with tangential views of the patello-femoral joint in 30 degrees of flexion should be taken. As well as identifying possible defects an assessment of joint alignment can be made.

Radiographs of osteochondritis dissecans may show the lesion as a well - circumscribed area of sclerotic subchondral bone separated from the remainder of the epiphysis by a radiolucent line. Old traumatic lesions often have a similar appearance on a plain radiograph.

In the case of osteochondritis dissecans of the knee a number of systems have been devised to evaluate radiographs. Harding described a system where 2 lines are drawn on the lateral radiograph, the first along the posterior femoral cortex and the second along the Blumensaat line (corresponds to the intercondylar notch). The articular surface between these two points represents

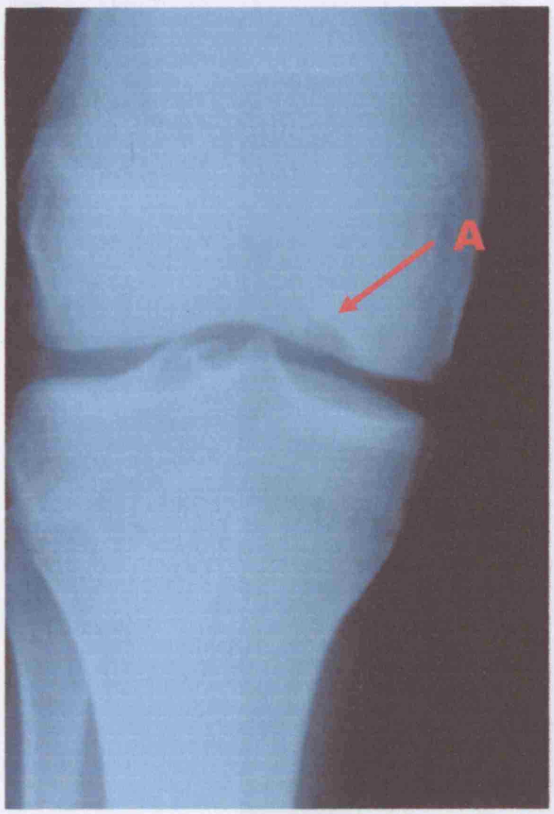

Figure VIIa. AP radiograph demonstrating an osteochondral defect (A) of the medial femoral condyle.

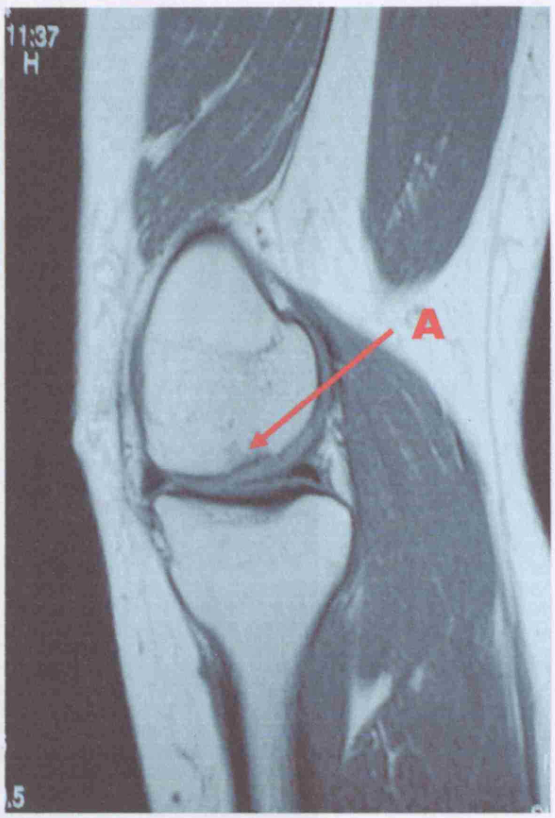

Figure VIIb. MRI (T1 weighted) of the same knee as in figure VIIa (sagittal view) demonstrating an osteochondral defect (A) of the medial femoral condyle with underlying 'bone bruising'.

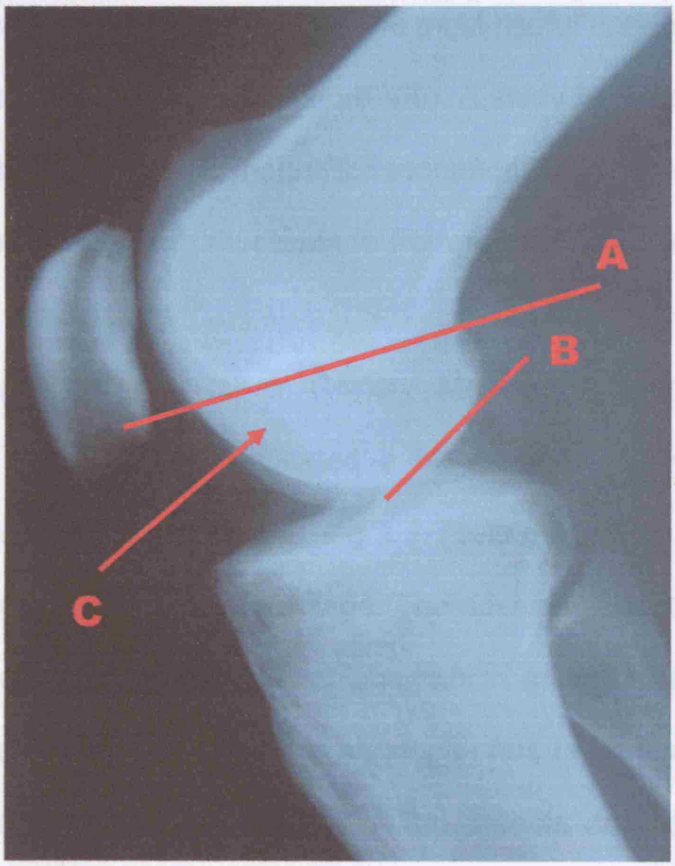

Figure VIII. Lateral radiograph of the knee demonstrating the Blumensaat line (A), and a line drawn along the posterior femoral cortex (B). Between these 2 lines Harding found a high incidence of osteochondritis dissecans (C).

the most common site for osteochondritis dissecans lesions on the medial femoral condyle (figure VIII)[76].

However in the majority of cases osteochondral defects of whatever cause are hard to identify on a plain radiograph [77].

Magnetic Resonance Imaging

Magnetic Resonance Imaging is currently the most useful non-invasive imaging technique for evaluating the knee [78], figure VIIb. A study by Dipaola et al found that the observations made from magnetic resonance images of osteochondritis lesions correlated closely with those made from an arthroscopy but correlated poorly with plain radiographs [79].

The International Cartilage Repair Society Magnetic Resonance Imaging Committee met in 2000 and suggested a fat saturated T1 weighted GRE (Gradient Recalled Echo) sequence using a 1 Tesla magnet or greater as one of the best sequences at imaging cartilage. The advantage of this sequence is the excellent contrast between the cartilage, which appears bright, and fluid, bone and fat which appears dark. This sequence has been shown to be very accurate in detecting cartilage defects [80]. The defects are seen as contour defects unlike fast spin echo sequences that appear as signal abnormalities. The use of fat suppression increases the dynamic range of signal intensities within the articular cartilage allowing the detection of more subtle changes in signal intensity. Also fat suppression eliminates the chemical shift artifact and reduces the motion-induced ghosting artifact from extra-articular fat signals [81]. With increasing the strength of the magnet the resolution of the image improves [82].

The environment within the joint also influences the detection of defects by MRI. Kramer et al noted that detecting lesions using an MRI scanner was made

easier in the presence of an effusion due to the orthographic effect of free fluid in the joint on T2-weighted images [83]. The detection of detached osteochondral fragments are also made easier in the presence of free fluid such as an effusion [84].

As well as detecting specific defects in the articular surface current MRI techniques are looking at the characteristics of cartilage itself. The water content of cartilage can be deduced using an MRI. This relatively new application of MRI could be extremely useful, since it is thought that increased hydration is an early indicator of disease, however these changes are small (< 5%) and therefore difficult to detect [82]. Another possible avenue for development is the use of contrast agents. Magnevist or Gadolinium-$DTPA^{2-}$ (Diethylene Triamine Penta-Acetic Acid) is an ionic agent that has a negative charge and that is able to penetrate cartilage. This contrast agent works since glycoaminoglycans (GAG's) also have a negative charge so areas within cartilage that have a high GAG content will have low concentration of Gd-$DTPA^{2-}$ and areas with a low GAG content will have a high concentration of Gd-$DTPA^{2-}$. From the distribution of Gd- $DTPA^{2-}$, areas of high and low GAG concentration can be determined. This technique is called 'delayed Gadolinium Enhanced MRI of Cartilage' (dGEMERIC) and is illustrated in (figure IX). The results of this technique are encouraging when compared to the 'gold standard' of estimating GAG content biochemically and histologically [85]. This agent also appears to increase the detection rate of defects as apposed to using an MRI with a non-ionic contrast such as Prohance (Bracco Diagnostics, Princeton, New Jersey) [86]. Using the dGEMERIC technique one cannot make an absolute measure of the GAG content, but it provides a baseline with which disease progression and therapeutic measures can be monitored.

The techniques described above enables the detection of abnormal cartilage before it breaks down to form a defect within the articular surface. With early detection of 'problem areas' of cartilage possible preventative or disease reversing techniques could be introduced. As yet these novel MRI techniques are not being used in routine clinical practice.

Along with detecting defects in the articular surface, a number of useful observations can be made of the bone underlying the lesion. The degree of penetration into the subchondral bone can be estimated and the presence of bone oedema can be observed. The presence of bone oedema can be useful in monitoring the success of therapeutic measures and disease progression. MRI can exclude other intra articular pathologies such as ligamentous disruption or meniscal tears.

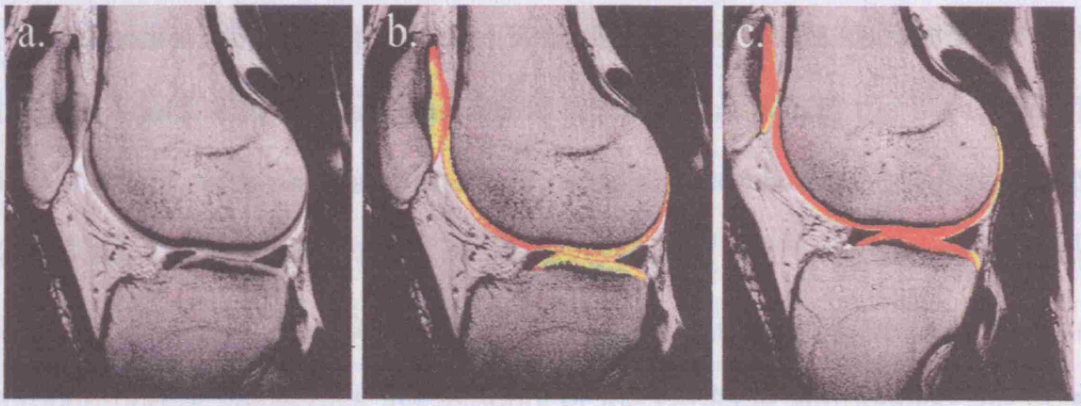

Figure IX. This sequence of magnetic resonance images illustrates how dGEMERIC imaging can visualize the glycosaminoglycan composition of articular cartilage.

IXa, Shows a proton density image of articular cartilage.

IXb, Following administration of a charged ionic contrast agent (Gd- $DTPA^{2-}$), the distribution of which is dependent on the concentration of glycoaminoglycans (GAG's). Areas of high concentration of GAG's take up less of the contrast due to there negative charge and areas of relatively low GAG content will take up more of the contrast.

IXc, When the same patient is given a nonionic agent (Gd(HPDO3A) the cartilage appears homogenous. This suggests that the selective uptake of the ionic contrast agent seen in IXb is due to charge and hence indicates the GAG distribution [82]. (Courtesy of the American Journal of Bone and Joint Surgery

At present although there are many exciting developments in the imaging of cartilage using MRI, their chief use is in detecting defects and assessing the integrity of implants post cartilage transplantation.

Arthroscopy is at present the most useful diagnostic tool enabling the investigator to visualise the joint surface. In the case of a suspected osteochondral defect the procedure is performed using the standard technique through lateral and medial parapatellar portals. The site of the defect can be noted as well as the size and depth of the defect. At this stage the extent of the lesion can be graded (from 1 to 4) according to the International Cartilage Repair Society (ICRS) Grading System (table I). Using a probe introduced through one of the portals the integrity of the cartilage surrounding the defect can be assessed. It is also important to assess the rest of the knee for similar defects in the articular surface and other potential causes for the patient's symptoms should be excluded.

In summary the management of a suspected osteochondral defect should include a detailed history and examination together with plain radiographs of the knee and an MRI scan. Following these investigations, the presence of an osteochondral defect can be fully assessed by performing a knee arthroscopy.

Management of chondral and osteochondral defects in the knee

Non-surgical Treatment

As mentioned earlier in this review, children with osteochondral defects no larger than 2-3 cm in diameter with open physes are best managed conservatively for the first six to twelve months since the majority of their defects will heal. In the case of adult patients with symptomatic defects, non-surgical, conservative management probably has a limited role. Non-surgical options include a period of protected weight bearing following an acute injury and a course of non-steroidal anti-inflammatories. Physiotherapy may help regain range of motion after an injury and improve quadriceps strength.

This line of management is probably best reserved for superficial injuries that do not penetrate the tidemark and are asymptomatic. Long-term follow-up studies of superficial injuries have not demonstrated progression to degenerative disease [87] [88].However there remains the concern that significant injury to the articular surface may progress leading to increasing pain and disability especially in athletic individuals. For this reason surgical options should be considered in adult patients with full thickness defects who are symptomatic.

Surgical Treatment

Over the years many techniques have been tried and tested with varying degrees of success. These include arthroscopic lavage and debridement of damaged articular cartilage, techniques that penetrate the subchondral bone, osteotomies, periosteal or perichondral grafting, autogenous osteochondral grafting (mosaicplasty), massive osteochondral allografts, autologous chondrocyte transplantation and the use of mesenchymal stem cells. Synthetic implants have also been used, such as carbon fibre pads.

The main difficulty in comparing these various techniques is the lack of established criteria for determining a successful result. Many publications quote success in terms of excellent, good, fair and poor results but based on different classification systems [89-91]. The difficulty at present is developing a reliable and reproducible classification system with no inter- or intra- observer error which also takes into account additional factors such as site, size, depth and location of defect, together with other co-existing injuries.

TECHNIQUES

Arthroscopic Lavage and Debridement

The benefit of simple lavage was discovered by chance by Burman in 1935 but it was Jackson and Bauer who pioneered arthroscopic lavage for incomplete lesions of articular cartilage [92]. However a possible placebo effect has been noted in the literature [93]. The symptomatic benefit from this technique is thought to be due to the removal of loose articular debris and inflammatory mediators known to be produced by the synovial lining of damaged joints. Evans et al [94] demonstrated in their study that the intra-articular injection of allogenic cartilaginous particles into rabbit knees resulted in synovitis and stiffness with concomitant destruction of articular cartilage which explained the beneficial effects sometimes observed in patients after lavage. Jackson et al [24] showed that lavage could benefit patients with symptomatic defects with 45% of patients reporting an improvement at 3½ years. Better results were seen when debridement (removal of loose fragments of cartilage) was performed as well as lavage. In a review of 137 patients, 88% experienced improvement with 68% continuing to have some benefit at 3 years.

Hubbard [22] reported in a prospective randomised trial comparing arthroscopic debridement with washout that at 1 year the mean improvement in a modified

Lysholm score was 28 for the debridement group but only 5 for the washout group. At 5 years the mean improvement for the debridement group was 21 but only 4 for the washout group. In this report Hubbard does not mention the defect size and all defects were located on the medial femoral condyle, an area of the knee that responds well to treatment. He does not comment on whether the defects progressed in terms of joint space narrowing on follow-up radiographs or at follow-up knee arthroscopies.

Debridement and washout at best only gives short term relief without addressing the underlying pathology. There is the concern that damage to articular cartilage be extended by the debridement and may progress in an active patient who continues to perform high impact loading through the site of injury. For this reason this treatment has little role in the management of isolated full thickness defects in articular cartilage in the young active patient.

Techniques that penetrate the subchondral bone – 'marrow stimulation'

There are various techniques of subchondral bone penetration, which are used to encourage a repair of the defect. By penetrating the subchondral bone numerous pluripotential mesenchymal stem cells are released together with some bleeding into the defect. The resulting blood clot fills the defect and with time differentiates into a fibrocartilaginous repair.

1. Subchondral Bone Drilling

Pridie observed in the late 1950's that patients who had had drilling to the base of a cartilage defect had developed a smooth fibrocartilage cover over the base of the defect on subsequent re-exploration [95]. The procedure is still very much in use today. At arthroscopy once the lesion has been identified and debrided,

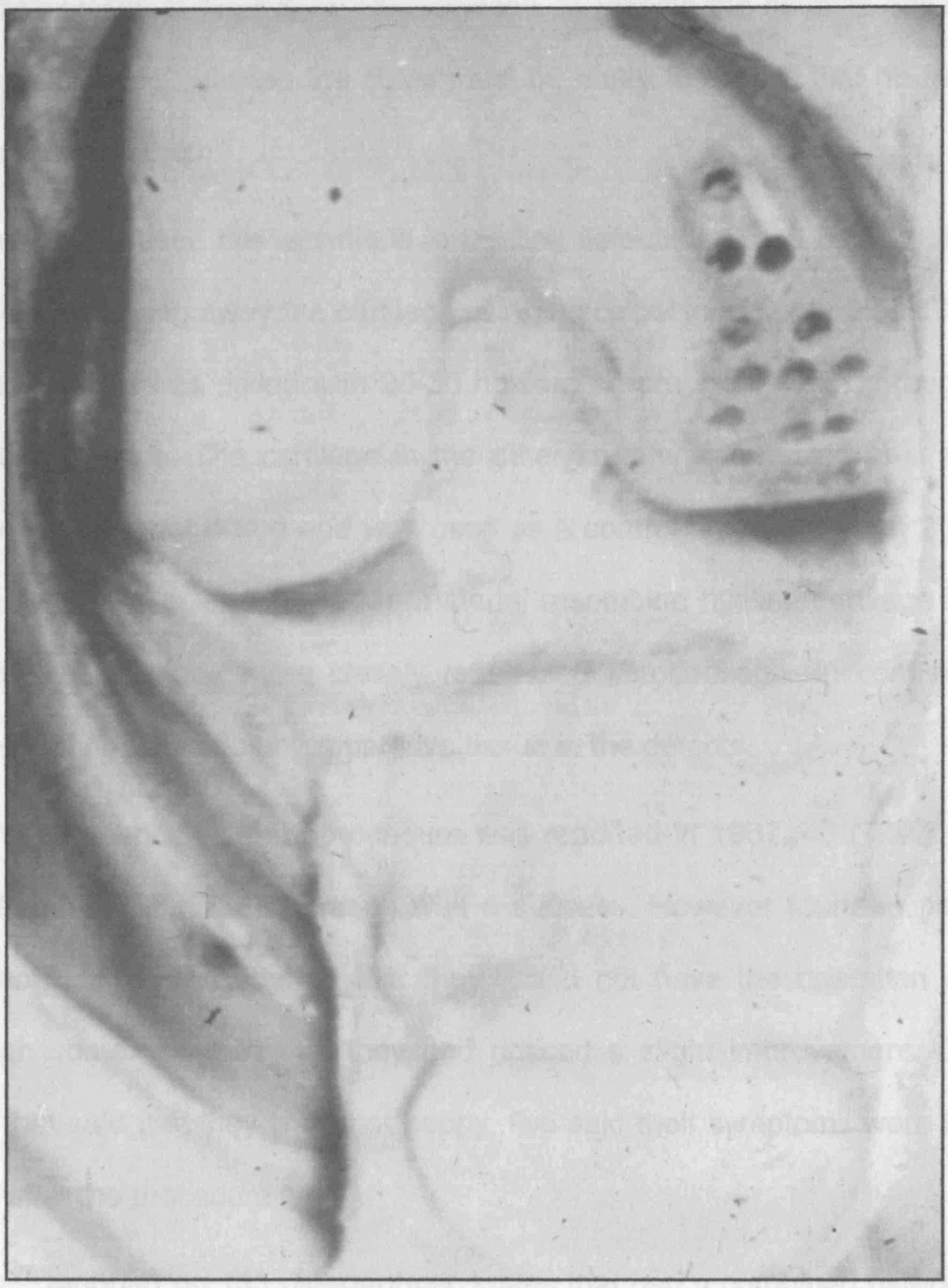

Figure X. Drilling of an osteochondral defect following debridement of a defect over the medial femoral condyle [2]. (Courtesy of the British Journal of Bone and Joint Surgery).

a 2 mm Kirschner wire is used to drill multiple holes into the highly vascularised subchondral bone (figure X). This encourages a bleeding response that ultimately results in healing by fibrocartilage. In placing the multiple drill holes, adequate spacing between the holes must be made to ensure that no fracture occurs between them[96].

Mitchell et al [27] used this technique in treating defects that had been artificially created by scraping away the cartilage using a scalpel in mature rabbits. In one knee the defect was drilled with 20-30 holes of 1 mm in diameter through the subchondral bone. The cartilage in the other knee was removed in a similar fashion but was not drilled and was used as a control. Interestingly at 2 and 4 months after the drilling the repair material resembled hyaline cartilage but at 12 months the repair more closely resembled fibrocartilage. In contrast the controls did not develop any reparative tissue in the defects.

Pridie's experience with the procedure was reported in 1967, 46 (77%) out of 60 patients felt that the operation was a success. However fourteen patients were not happy and reported that they would not have the operation again, although some admitted that they had noticed a slight improvement. Of the group that said that they were not happy, five said their symptoms were in fact worse after the procedure [2].

Tippet [97] reported on 133 osteoarthritic knees that had a combined osteoplasty and osteotomy. The osteoplasty was performed by removing the damaged cartilage and then drilling multiple holes 3-4 mm deep and 2-3 mm apart. Tippet advised drilling at a slight angle to increase the surface area for forming cartilage as well as offering some sort of protection to the fibrous clot from disruption when the knee flexes and extends. The results at a mean of sixty-two months follow up revealed that 70.8% had excellent results, 15.4% good, 6.9%

fair and 6.9% poor, with complete pain relief in 68.5%. These results were reported as superior to that of osteotomy alone [97].

Childers et al [19] reviewed 25 patients with chondromalacia patellae who had a partial chondrectomy and drilling to the defect following failed conservative treatment. The damaged articular cartilage over the retropatellar surface was excised down to the subchondral bone and then multiple small holes were drilled into the defect. Patients were allowed to partially weight bear with two crutches as soon as comfort allowed. Twenty-two of the 25 patients achieved good or excellent results at a mean follow up of 24 months. The authors noted that two of the three failures were over thirty years of age.

In 1978 Bentley [53] reported 56% satisfactory results following cartilage excision and drilling of he subchondral bone for grade II defects (Outerbridge [54]) attributed to chondromalacia patellae. The mean follow up was seven years. Lesions that were more extensive than grade II, produced unsatisfactory results in this patient group.

In summary, short-term results appear good in patients noticing an improvement in their symptoms especially with small lesions but long-term follow up results are disappointing [53].

2. Abrasion Chondroplasty

The abrasion technique involves using a motorised burr to abrade through the full thickness of the damaged cartilage down to the subchondral bone to precipitate bleeding and the release of mesenchymal stem cells from the marrow.

Kim et al [98] performed a study using a rabbit model to compare chondral shaving with abrasion chondroplasty. With chondral shaving a motorized

shaver was used to excise an area of cartilage leaving as smooth a surface as possible (partial thickness). The results revealed that none of the defects that were produced by shaving filled with repair tissue at 4 or 12 weeks. However, in the case of abrasion chondroplasty using a motorized burr to abrade through the full thickness of the cartilage down to subchondral bone, repair tissue was found to fill the defect in 17 out of 19 animals at 4 weeks and 18 out of 20 at 12 weeks. This study also assessed the effects of continuous passive motion. It was observed that the animals in the abrasion group who had continuous passive motion had defects that completely filled with repair tissue and those that had intermittent active motion the defects only partially filled. The nature of the repair tissue following abrasion ranged from fibrous to hyaline like cartilage at 12 weeks.

Concerns have been raised that the use of a rotary burr to abrade cartilage may cause thermal necrosis of the underlying bone [99], although abrasion did not appear to effect the repair in Kim's study.

Johnson [25] reported on a series of 95 patients with a mean age of 60 years, who had changes on knee radiographs consistent with degenerative arthritis. At a minimum of 2 years post abrasion chondroplasty, 74 patients said they were better, 15 said they were worse, 7 were the same and 3 failed to answer. At the same follow-up, 64 patient knees had comparisons made between their pre and post-operative standing AP radiographs. Half were reported to have wider joint space, which was attributed to a fibrocartilage repair. Johnson did not report on those patients who had a wider joint space on their postoperative radiograph, whether they noted an improvement in their symptoms. The author concluded that this procedure was best reserved as a palliative technique in patients with rest or night pain who were not particularly active.

Friedman et al [100] published results following a retrospective study of arthroscopic debridement and abrasion chondroplasty. He found a 60% improvement in patients post surgery at a mean follow up of 12 months and found the best results in patients under 40 years. From their experience of the technique they noted an advantage over other techniques in that difficult to reach areas such as the patellofemoral joint using the drilling technique can be readily accessed by the abrader.

Bert and Maschka [17] performed a retrospective review of 126 patients who had abrasion arthroplasty plus arthroscopic debridement or arthroscopic debridement alone. Mean follow-up was 60 months. In the group treated with abrasion, 51% had good or excellent results, 16% fair and 33% poor results. The remaining patients who had arthroscopic debridement alone 66% had good to excellent results, 13% had fair and 21% poor results. The interesting observation made in this study was there appeared to be little correlation between the patients' symptoms in terms of pain and disability with the extent of the patients' pathology. A prime example was a patient who had a good cover of fibrocartilage following an abrasion chondroplasty yet clinically complained of intense pain and required a prosthetic joint replacement. Hence the results of this technique appear unpredictable. Bert went on to conclude that although debridement of defects can reduce symptoms, abrasion arthroplasty does not appear to benefit patients who have osteoarthrosis of the knee and may even increase their symptoms.

The majority of long-term follow up studies for abrasion chondroplasty have been performed on patients with osteoarthritis rather than isolated osteochondral defects. The unpredictable results mentioned above are almost certainly due to the co-existing factors of diffuse knee joint involvement, which

occur with arthritis. Johnson [25] considered this procedure as palliative in patients with a degenerative knee condition who are not particularly active. There are better alternatives to the technique in the management of patients with discrete osteochondral defects with no evidence of arthritis.

3. Spongialization

Ficat et al [20] described an extension of the technique that Pridie [95] pioneered although not too dissimilar from the abrasion technique described above. This entailed resecting en block all of the diseased cartilage with its underlying subchondral bone, leaving a completely exposed cancellous bony bed. The authors called this technique 'spongialization' since it exposed the 'spongiosa' found beneath the subchondral bone. They considered it necessary to remove the entire subchondral bone underneath the damaged cartilage since it too was abnormal. By removing the highly innervated subchondral bone associated with the damaged articular cartilage, they supposed that the pain would be alleviated. They felt that the depression created by the technique was important since it created an area, which could be filled with repair tissue without affecting the mechanics of the joint. They reported on 85 patients who underwent the procedure for chondromalacia patellae, 79% had a good or excellent result at a mean follow up of 15 months. However despite these encouraging results there are no long term follow-up reports in the current literature.

4. Microfracture

This technique has similarities to the subchondral bone drilling described by Pridie [95] in that the aim is to penetrate the subchondral bone provoking bleeding and healing by fibrocartilaginous repair. An arthroscopic awl (figure

XIa) is used to make the microfractures (figure XIb). This procedure for repairing defects is thought to cause less thermal necrosis of the underlying bone and surrounding tissues compared with a motorized burr for example. As previously described, the area of damaged cartilage should be removed before microfracturing commences [101]. There have been reports that this technique is able to generate repair tissue, which is made up of a mixture of hyaline and fibrocartilage and found to completely fill the defect [31].

Steadman et al [31] reported pain relief at 3 to 5 years in 75% of patients, although 20% remained unchanged and 5% were worse. An assessment of activities of daily living revealed an improvement in 67% of patients with no changes in 20%, the remaining 13% were made worse. Patients who played sports and other high activity pursuits noted an improvement of 65%.

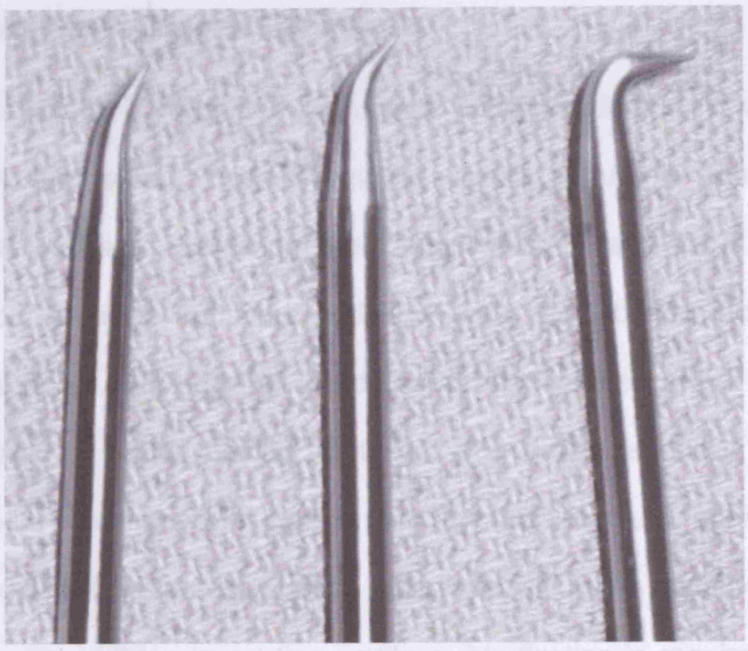

Figure XIa. Photograph of arthroscopic awls with conical shape angulations of 30°, 45° and 90° [102].(Courtesy of the American Journal of Bone and Joint Surgery).

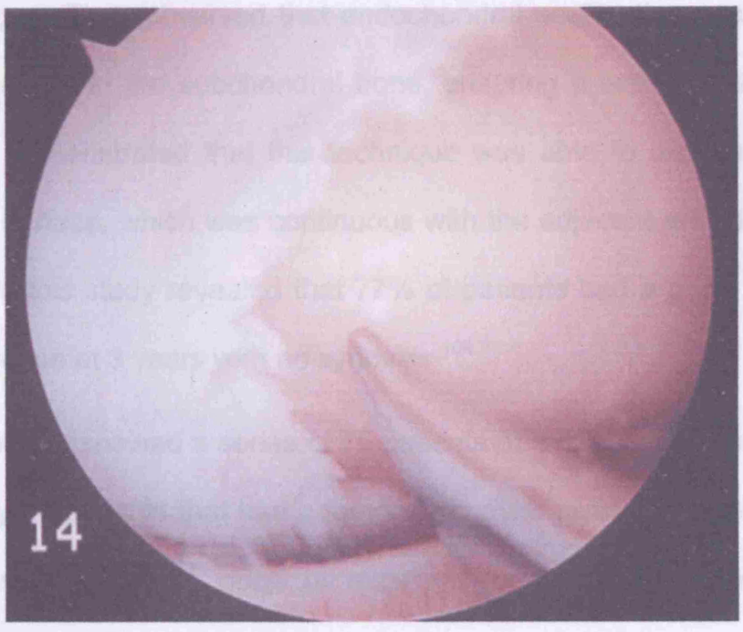

Figure XIb. Picture taken at arthroscopy showing the microfracture technique to a defect over the medial femoral condyle[102].(Courtesy of the American Journal of Bone and Joint Surgery).

Carbon Fibre Matrix Support Prostheses

Muckle and Minns [103] reported the use of a woven carbon fibre pad as a scaffold for supporting fibrocartilaginous repair tissue in the repair of osteoarthritic cartilage. Following the identification of a suitable defect the damaged cartilage is removed and the area is debrided down to the subchondral bone. The edge of the defect is then probed and if unstable is debrided back to stable, healthy cartilage. The defect is drilled to provoke bleeding and a patch of woven carbon fibre that has previously been cut to size is positioned within the defect. Care is taken to position the edges of the patch beneath the rim of the surrounding cartilage. No fixation is required since the carbon fibre pad is a 'press-fit ' and becomes impregnated with blood clot within a few minutes of tourniquet release, securing the pad to the defect. Muckle and Minns reported that both animal and clinical studies showed that the carbon fibre pads became filled with strong fibrous tissue made up of predominantly type I collagen. They observed that endochondral ossification occurred within the pad adjacent to the subchondral bone, ensuring a secure fixation for the graft. They demonstrated that this technique was able to produce a smooth conforming surface, which was continuous with the adjacent articular cartilage. Results from this study revealed that 77% of patients had a good or excellent clinical response at 3 years with no synovitis [104].

Bentley et al [105] reviewed a series of 79 patients at a mean follow up of 6 years post surgery. In patients that had a femoral condylar repair 77% had a good or excellent result with 93% good or excellent for those with medial femoral condyle defects. However, repairs to patellar defects were less successful with only 49% with good or excellent results and 20% who required patellectomy. A study by Meister et al [106] reported on 27 patients with painful articular defects of

the patella who underwent this technique. The mean age of the patients (8 male, 19 female) was 29.8 years with a mean defect size of 2.1 cm^2. There were 4 excellent, 3 good, 7 fair and 13 poor results. Nine patients subsequently had a patellectomy for persistent pain at a mean of 27 months after surgery. Patient satisfaction was 41%. On review of the grafts at arthroscopy the results were encouraging with good incorporation of the carbon fibre pads. However, the poor clinical outcome together with seeding of the joint with carbon fibre debris and histiocytic giant cell reaction in the synovium were cause for concern.

This repair is thought to give a firmer repair than more traditional procedures such as drilling, abrasion chondroplasty and microfracture. Although initial results were encouraging there are concerns about the long- term viability of such a repair.

Osteotomy

Osteotomies can be performed alone or with other techniques in the treatment of osteochondral defects or unicompartmental osteoarthritis.

Limb malalignment is a significant predisposing factor for the development of osteochondral defects. Maquet et al [107-109] showed with varus knees, loads through the medial compartment were greater than those through the lateral compartment. Thus, genu varum may cause progressive articular cartilage damage. It was reasonable to assume that correcting the varus deformity would stop this progression. Re-alignment surgery to correct a varus or valgus deformity can redistribute load bearing through intact articular cartilage rather than through the damaged area. Osteotomies can be performed either above or

below the knee in the form of an opening or closing wedge distal femoral osteotomy or high tibial osteotomy. The choice of osteotomy depends on the site of the deformity.

Jackson and Waugh [110] were the first to publish results of the upper tibial osteotomy. In total 11 patients with a mean age of 60 years were reviewed over a 6 year period, with a mean follow up of 31 months. The indications for surgery in all patients was a disabling pain attributed to osteoarthritis unrelieved by conservative treatment, a valgus/varus deformity and a range of knee flexion greater than 90°. Of the 11 patients, 7 had a valgus and 4 had a varus malalignment. The osteotomy was performed through cancellous bone at the level of the tibial tubercle. The fibula was also divided through a separate incision over its middle third. Initially, the tibial osteotomy was outlined by a series of drill holes and was competed with a gouge. The soft bone allowed easy angulation and no internal fixation was used. The leg was immobilised post operatively in a long leg plaster cast. Post-operative radiographs were performed to confirm satisfactory alignment and the plaster was wedged if necessary. Weight bearing was allowed after 4 to 6 weeks. At 8 to 10 weeks the knee was mobilised and most patients achieved 90° of flexion at 2 to 6 weeks from the time the plaster was removed. All patients reported considerable improvement in their pain, with all but 1 patient gaining satisfactory range of movement. I patient died in the first year due to unrelated causes.

Coventry [111] advocated this approach since it involved bone that would heal rapidly, allow early motion of the knee and early weight bearing and allowed exploration of the knee at the time of the osteotomy if required. Coventry's early results from 1 to 4 years after surgery reported 12 out of 22 patients had

satisfactory results, 1 patient who died of unrelated causes, 6 patients who had been operated on too recently to be evaluated and only 3 patients who reported an unsatisfactory result [111].

Subchondral bone, which is highly innervated, becomes sensitive to pressure if the overlying cartilage is softened or damaged. Osteotomies may relieve pain by reducing the pressure on damaged articular cartilage and so reduce the load transmitted to the underlying bone.

Bergenudd et al [112] reported on 19 patients with degenerative disease of the medial compartment of the knee. A proximal tibial closing wedge osteotomy was performed using a metal staple fixation (Figure XII) on the lateral side aiming for 4° of valgus over correction. A biopsy was made after a mean follow up of 26 months, 9 of the 19 patients showed signs of a fibrocartilage repair, 8 patients did not show any change and 3 showed evidence of deterioration. A clinical evaluation at 2 years revealed 14 patients had good or excellent results.

There was no correlation between the finding of a fibrocartilaginous repair and relief of symptoms. There was also no correlation between the clinical result and radiographic observations and the post operative varus-valgus angle.

Ivarsson, Myrnerts and Gillquist [113] reported on 81 knees at a mean follow up of 5.7 years and 65 knees at a mean follow up of 11.9 years that underwent a closing wedge tibial osteotomy with staples, for medial compartment osteoarthritis of the knee. At 5.7 years, 57% of patients reported a good result and 78% acceptable. At 11.9 years, 43% reported a good result and 60% acceptable. There was deterioration of 20 knees. In most cases the deterioration occurred between 8 and 9 years post surgery. They also reported that overcorrection of 3-7° valgus gave the best results based on observations

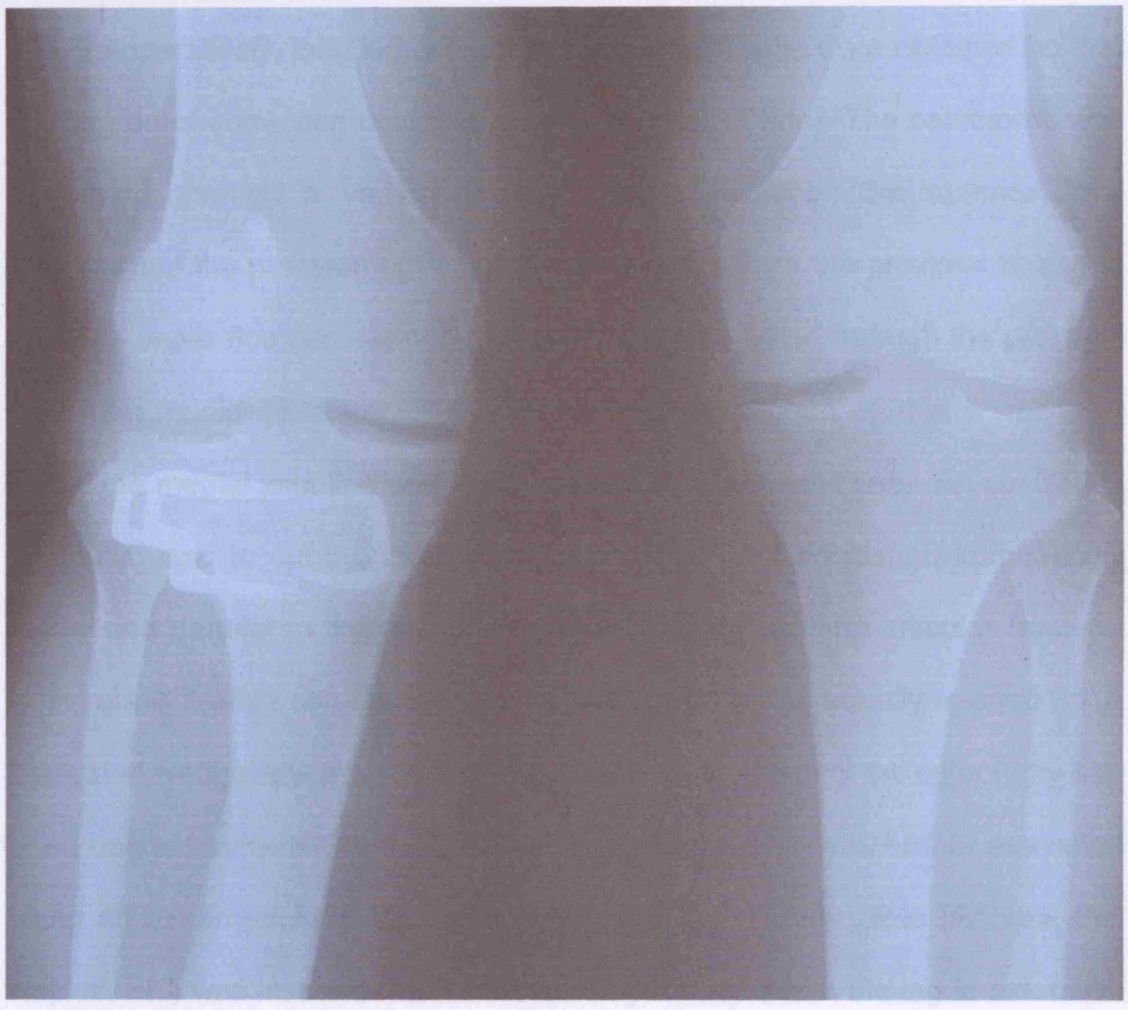

Figure XII. AP Radiograph taken whilst the patient was standing following a lateral closing wedge osteotomy of the right knee (patient previously had an anterior cruciate ligament reconstruction)

at 5 years post osteotomy.

An opening wedge high tibial osteotomy has also been described. Hernigou et al [114] and Moroni et al [115] have reported favourable results with this technique in patients with medial compartment osteoarthritis. More recently Puddu et al [116] made a modification to this technique which was later described by Fowler et al [117]. Pre-operatively, long leg, weight bearing radiographs were obtained so that the degree of correction could be estimated (Figure XIIIa). The osteotomy was performed through a vertical incision centred between the anterior tibial tubercle and the posteromedial border of the tibia. Once the proximal tibia was exposed under fluoroscopic control a guide pin was drilled through the proximal tibia from medial to lateral. The guide pin was positioned so that it was 4cm below the medial joint line and 1 cm below that lateral joint line. An oscillating saw was used to cut the medial cortex only and was positioned immediately below and parallel to the guide pin to help prevent an intra-articular fracture. Using small flexible osteotomes the osteotomy site was gradually opened up. A calibrated wedge was advanced into the osteotomy site until the osteotomy had been opened sufficient to correct the malalignment. This was further evaluated using an extramedullary alignment guide. A 4 hole Puddu plate (Arthrex, Inc, Naples, FL.) was inserted into the osteotomy site, and with the leg in extension it was secured with 2 cancellous screws proximally and 2 cortical screws distally (figure XIIIb). The majority of authors recommend bone grafting osteotomies greater than 7.5mm to prevent delayed or non union. Patients with an intact lateral cortex can partially weight bear in a cast brace from day 1, then fully weight bear at 6 weeks. Noyes et al [118] reviewed a total of 55 patients over

Figure XIIIa **Figure XIIIb**

Figure XIII Pre-operative (a) and post-operative radiographs (b) of a left knee showing a correction of a varus malalignment using an open wedge, medial, high tibial osteotomy with a Puddu plate (Arthrex, Inc, Naples, FL.)

a mean follow up period of 20 months where the osteotomy united in all patients, although 3 patients had a delayed union and 1 patient required revision since he mobilized fully weight bearing from the start resulting in the plate failing.

There has been some success with combined procedures. Tippet [97] reviewed 133 patients who either had a combined osteotomy and subchondral drilling or osteotomy alone. The combined group did better, although this was for unicompartmental osteoarthritis and not focal osteochondral defects. More recently osteotomies have been combined with chondrocyte transplantation techniques as a one stage procedure with encouraging results (unpublished data, RNOH).

The majority of studies have been published on osteotomies for osteoarthritis as apposed to discrete osteochondral defects and the long-term studies have been disappointing [119] [120;121].

However, with limb malalignment being one of the predisposing factors for the development of focal defects in articular cartilage, a corrective osteotomy can be useful in the management of these patients as noted by Minas and Nehrer [122] in their review of articular cartilage defects and their management .

All the techniques mentioned so far may result in the defects being filled with repair tissue that is predominantly fibrocartilage. It has been well established that the mechanical and biochemical properties of fibrocartilage are inferior to that of hyaline cartilage. It has poor resilience to compressive forces, poor wear characteristics and tends to breakdown with time. With this in mind considerable research has been undertaken to develop techniques that can fill

a defect in the articular surface with hyaline cartilage that can alleviate symptoms and give a long lasting repair.

Perichondrial and periosteal grafting

This technique takes advantage of the fact that the cambium layer of periosteum or perichondrium possesses multipotent mesodermal cells. Rubak et al [123;124] showed that free periosteal grafts transplanted to defects surgically created over the femoral condyles in rabbits could result in hyaline-like repair tissue that closely resembled the surrounding articular cartilage. Rubak concluded that the repair tissue generated was not only like normal articular cartilage but originated from the periosteum. Interestingly, the post-operative rehabilitation proved crucial on the nature of the repair. Immobilisation appeared to inhibit the development of a hyaline-like repair and mobilisation a stimulatory effect [124]. In the clinical setting there has been some success with this technique in treating degenerative metacarpophalangeal joints with rib perichondrium [125]. The problem with larger joints such as the knee for example is being able to attach the graft securely.

Early results for this technique using either rib perichondrium [126] or periosteum from an area adjacent to the tibial tuberosity were encouraging. However, more long-term follow-up has not been as encouraging. Augerman et al [127] reported that 9 out of 14 patients had severe or consistent pain at 8 years follow-up having had a periosteal graft. Arthroscopic or MRI assessment revealed that less than half of the defects were ¾ filled. Other studies have also documented similar poor long-term results [128].

The use of perichondrium has a significant limitation in the fact that it is largely found covering the cartilage between the sternum and the ribs. This limits the

graft size and often several ribs must be stripped to obtain sufficient perichondrium. Long-term problems encountered with perichondrium include endochondral ossification and delamination of the cartilage from the underlying bone [122]. For these reasons the role of perichondral or periosteal grafts alone in the treatment of osteochondral defects is limited.

Osteochondral Allografts

Osteochondral allografts tend to be used in the repair of large defects such as trauma cases, osteonecrosis or following excision of tumours [129]. The great advantage of using an allograft is that the shape of the graft can be matched to the exact contour of the recipient site, since the graft can be taken from the same location on the donor as the recipients' defect (orthotopic grafting). This overcomes the difficulty of trying to restore the normal contour of the articular surface by other means and also avoids the morbidity associated with harvesting large quantities of articular cartilage from the patient as in the case of a mosaicplasty.

With this technique comes the risk of transmission of infectious diseases such as HIV and Hepatitis B and C from the donor tissue. Before any allograft transplantation the donor is screened although the risk of disease transmission cannot be completely eliminated [130;131].

Another factor to consider with an osteochondral allograft is the possible reaction of the recipients' immune system. Articular cartilage is considered an immunologically privileged tissue [35]. This can be attributed to two reasons. The fact that articular cartilage is avascular isolates it from the immune system and although antigens are found on chondrocytes they are protected from exposure

to the recipient by their surrounding matrix [132]. If articular cartilage could be transplanted from donor to recipient without the attached subchondral

bone then no immunologic considerations would have to be made. However allografts must be transplanted with bone attached to secure them to the host bone [133]. Subchondral bone possesses many antigens, which could precipitate an immunologic rejection. Although freezing has been used to reduce this response it also reduces the number of viable chondrocytes in the graft [134 135].

The limited availability of fresh material for osteochondral allografting has resulted in considerable efforts in improving the viability of chondrocytes post freezing. Damage to cells through freezing is thought to occur as intra and extra-cellular water converts to ice crystals. This tends to occur between 0° and -40°. By gradually cooling cells at a rate slow enough to allow water to equilibrate across the cell membrane should ensure a minimum amount of intra-cellular ice to form. Following slow freezing down to -40°, more rapid freezing can then occur down to -80° [35].

Various agents have been used in an attempt to protect the chondrocytes from the effects of freezing with limited success. Dimethylsulfoxide (DMSO) is able to protect isolated chondrocytes but poorly penetrates the extracellular matrix of articular cartilage and so offers protection to cells in the superficial zone only [136].

Mahomed et al [137] reported on 91 patients who had fresh small fragment allografts for defects sustained following trauma in the knee. In this study, patients who required correction of a malalignment also had an osteotomy. At 5 years post-transplantation 75% of cases were reported as a clinical success, 64% at 10 years and 63% at 14 years. Unipolar grafts, involving only one

surface of the compartment had a lower failure rate compared with bipolar grafts and younger patients (less than 60 years) did better.

A study by Chu et al [138] reported on 55 patients of 45 years or less with a mean follow up of 75 months. Following unipolar grafts 76% had a good or excellent result and 50% for bipolar grafts.

Newman [35] in his review of the subject concluded that there were a number of factors important for the success of an osteochondral allograft; 1/ That the graft should be orthotopic, matching the exact surface contour and height of the recipient site and fixed firmly. Any unevenness in the surface is associated with a bad outcome; 2/ Young donors are preferable; 3/ Resorption of bone in the graft carries a poor prognosis.

Regarding the last point, in the majority of instances the bone underlying the cartilage in an allograft is dead and it has been postulated that the recipients' bone replaces the necrotic bone of the graft by 'creeping substitution', during the period of non-weight bearing post-operatively. Gross et al reported on 9 transplantations, that showed that the grafts united with replacement of the bony part of the graft by host bone with minimal collapse in only one case [139].

In summary there maybe an indication for osteochondral allografts as an alternative to prosthetic joint replacement in the management of young patients with large unipolar defects who lead an active life. However concerns remain about the long-term viability of the donor chondrocytes and the risks of the transmission of infection.

Autogenous osteochondral Grafting

A study by Outerbridge H.K. et al [140] reported on a small series of patients who had osteochondral defects over a femoral condyle repaired by plugs of cartilage and bone harvested from the patella. Once the defect had been identified at arthrotomy, the damaged area of the articular cartilage was excised down to cancellous bone using a narrow osteotome. The defect was shaped so that it had 4 walls perpendicular to the surrounding articular cartilage surface with bleeding cancellous bone at the base. The base of the defect was drilled with 5-10 holes of 2 mm in diameter and one of the walls of the defect was undermined. Using a saw a corresponding plug of cartilage with its attached subchondral bone was excised from the lateral facet of the patella and shaped to the contours of the defect and gently pushed into the defect. The surface of the graft was made flush with the rest of the articular surface. Post operatively the patients were placed on a continuous passive motion machine and were allowed brief periods of partial weight bearing. At a mean follow up of 6½ years post transplantation all 10 patients who were reviewed reported an improvement in their knee function and relief of their symptoms.

Hangody [141] described a technique in 1997 involving the transplantation of multiple osteochondral plugs for the treatment of symptomatic full thickness defects affecting the femoral or tibial condyles. At arthrotomy the damaged area of articular cartilage is located and excised and the surrounding cartilage is debrided back to a stable rim. The base of the defect is lightly abraded to promote fibrocartilage filling between the osteochondral plugs. A calculation is made based on the size of the defect to assess the number of plugs required to fill the defect. In the case of large defects multiple osteochondral plugs can be harvested. Using special instruments grafts are harvested from the extreme

medial or lateral aspects of the trochlea from the non- weight bearing area of the articular surface. Multiple drill holes are made in the base of the defect ensuring that they are perpendicular to the joint surface. The holes should be 2 mm deeper than they need to be to ensure that the grafts do not sit proud of the articular surface.

Smaller holes can be drilled between the larger ones taking care to leave enough intact bone between them. With the knee in flexion the plugs are guided into place by gentle impaction so that the surface of each graft lies flush with the rest of the articular surface (figure XIV).

Smaller grafts can be impacted between the larger ones. Once the surgeon is happy that the grafts are seated correctly the knee can be closed in the standard fashion. Patients spend up to 10 days with the knee immobilised in extension in a plaster cast [89]. Some authors advocate a period of non-weight bearing post surgery [142], whereas others recommend partial weight bearing from day 1 [89].

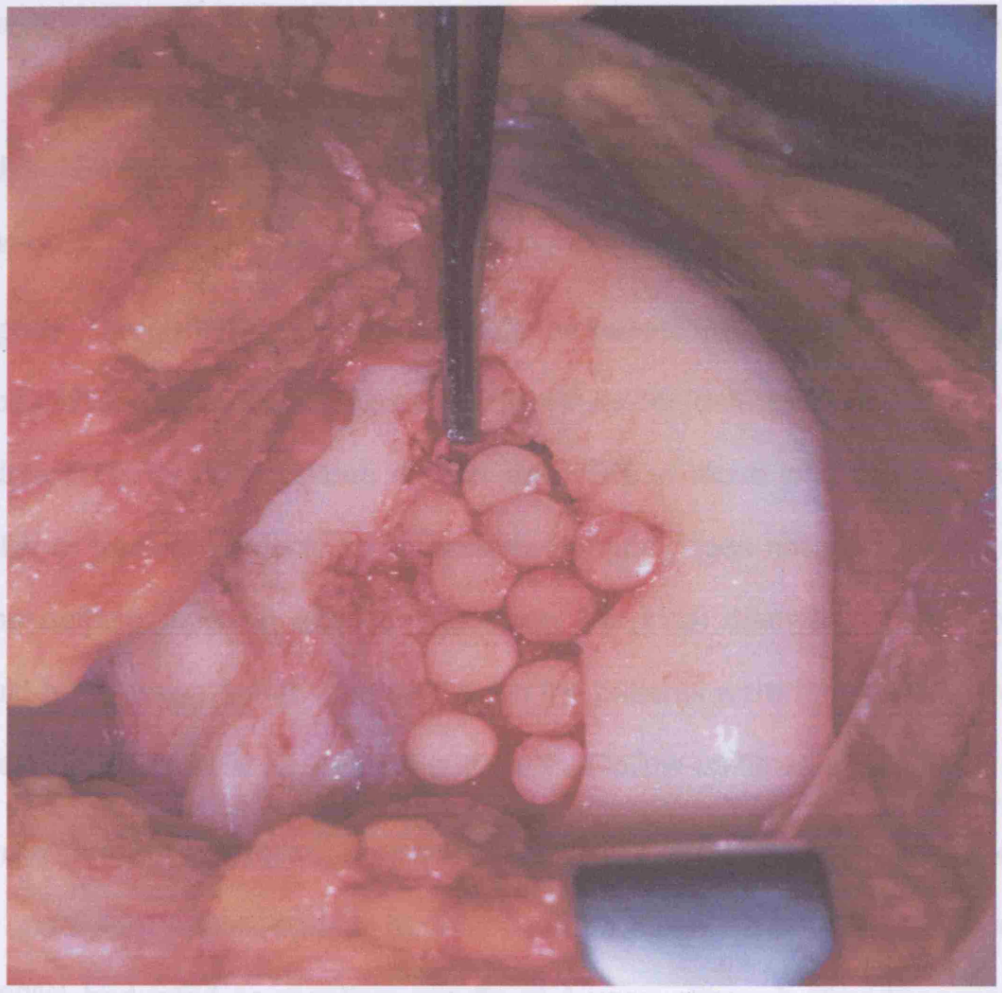

Figure XIV. An intra operative photograph following the transplantation of multiple osteochondral plugs to a defect over the medial femoral condyle.
(Courtesy of G. Bentley)

Hangody [143] reported encouraging results on 113 patients with more than 3 years follow-up. At a second look arthroscopy the donor sites had healed with fibrocartilage, none of the grafted cartilage plugs had displaced and biopsies showed that the plugs retained their hyaline character.

More recently Horas [142] reported on 20 patients treated with this technique, 16 had a lesion on the medial femoral condyle and 4 on the lateral femoral condyle. Seventeen patients reported substantial improvements at 2 years follow-up.

Hangody [144] reported on his recent results on patients reviewed over a 10 year period, 92% reported good to excellent results for defects over the femoral condyle, 87% for tibial plateau defects and 79% of those who had repairs to patellar or trochlear defects. Unfortunately Hangody does not mention the size of the defects repaired although does say the ideal diameter of the defect should be between 1 and 4 cm^2. Although the patients were followed up over a 10 year period there is no mention of the mean follow-up time.

In a randomized, controlled, clinical trial Bentley et al [89] reported on 42 patients who underwent a mosaicplasty to defects with a mean defect size of 4.66cm^2 , 29 (69%) had good or excellent results at 1 year, although they appeared to deteriorate with time. Arthroscopic examination revealed fair or poor results in 66% of patients. Five patients had mosaicplasty to the retropatellar surface, none of which had a good result. It was suggested that the poor results in the case of the patellar defects could be attributed to the differing thicknesses of donor and recipient articular cartilage.

The inherent weakness for this technique is that the gaps between the osteochondral plugs heal by less resilient fibrocartilage. In all cases in this study the harvest sites had healed with a fibrocartilage repair.

The majority of studies published to date have a short follow-up with only a few long-term studies. With the concerns of donor site morbidity and poorer results for patellar defects this technique may have a limited role in the management of small defects over the femoral and tibial condyles.

Bentley et al reported on patients with a mean defect size of 4.66 cm^2, Hangody mentioned that the ideal defect size should be between 1-4cm^2 but didn't mention the mean defect size in his results. This suggests mosaicplasty probably does not have a role in the management of defects of 4 cm^2 or larger.

This technique should probably be avoided in patients with bipolar lesions affecting both joint surfaces due to the concerns of the grafts dislodging as they catch one another with flexion and extension of the knee.

Autologous chondrocyte implantation in the knee

The aim of any cartilage repair technique is to relieve the patients' symptoms, restore the articular surface and prevent progression to early osteoarthritis. Articular hyaline cartilage has many unique characteristics that enable it to withstand very high compressive forces and shearing stresses. Therefore any substitute for articular cartilage must possess characteristics as close to that of hyaline cartilage as possible. A number of techniques have already been described which endeavour to replace the defect with hyaline cartilage such as osteochondral allografts and autogenous osteochondral grafts. There has been some success with these techniques but concerns such as disease

transmission in the case of allografts and harvest site morbidity in the case of autogenous grafts remain.

The origins of autologous chondrocyte implantation can be traced back to 1965 following the isolation of adult articular chondrocytes in suspension by Smith [145]. In 1968 Laurence and Smith demonstrated that isolated epiphyseal articular chondrocytes survived when implanted into fractures in rabbits[146]. Bentley and Greer [147] went on to show that isolated chondrocytes could be used for repairing defects of the articular surface in an animal model. In this study chondrocytes were taken from rabbits before they had reached skeletal maturity because of the ability shown by Mankin [7;8] that these chondrocytes were able to divide. However, once past skeletal maturity chondrocytes more or less lost this ability. Bentley and Greer [147] demonstrated that both isolated epiphyseal and articular chondrocytes could be used to repair articular cartilage defects.

The next stumbling block was to be able to expand the number of chondrocytes ensuring that the cultured cells retained their ability to produce type II collagen. Green [148] described a technique of culturing chondrocytes after they had been isolated from the extracellular matrix by enzymatic digestion. During the expansion, the cells gradually dedifferentiate and lose their ability to manufacture type II collagen, however they regain this ability once exposed to agarose gels [149]. Aston and Bentley showed that by growing chondrocytes at high density the phenotype was preserved and the cells produced type II collagen [150].The ability to expand the numbers of adult chondrocytes in a monolayer culture proved a significant advance in the treatment of osteochondral defects using autologous cells. Peterson et al [151] reported on the repair of defects in skeletally mature rabbits with autologous or homologous

cultured chondrocytes. Cartilage plugs were removed from the mid patellae and enzymatically digested and grown in a monolayer culture for 2 weeks. Then pellets of chondrocytes were implanted into artificially created defects and covered with either a layer of fascia, synovium, blood clot, tendon or periosteum. Results were encouraging with a total reconstitution of full thickness 3 mm defects with hyaline cartilage. In 1987 Grande et al [152] reported on an animal study using autologous chondrocytes grown in vitro, 82% of the defect was reconstituted with repair tissue compared with 18% in the ungrafted controls. To keep the chondrocyte suspension within the defect the cells were injected under a periosteal flap, which had been sutured to the rim of the defect. Using autoradiography it was established that the repair tissue had labeled cells incorporated within it. From these results it could be concluded that the implanted cells had a part to play in the formation of the repair tissue.

Brittberg et al reported on 23 patients treated with this technique. None of the defects extended beyond the subchondral bone. Patients' symptoms included pain, locking, swelling and retropatellar crepitus. The mean age of the patients was 27 years and the mean defect size was 3.1 cm^2. The procedure is divided into 2 stages. At the first stage 300-500 mg of cartilage is harvested arthroscopically from a minor load bearing area of the upper medial femoral condyle of the damaged knee. Care should be taken to ensure that a full thickness piece of cartilage is removed without damaging the deep layers of the specimen and not to violating the subchondral bone [129]. The specimen is then removed from the knee via one of the arthroscopy portals. The cartilage biopsy is then put into a sterile container and transferred to a laboratory. In the laboratory the specimen is enzymatically digested releasing the chondrocytes, which are then grown in a monolayer culture. The patient is readmitted 21–28

days following the harvest of cartilage and the second stage of the procedure is performed. To ensure a bloodless field a tourniquet is applied and a medial or lateral parapatellar arthrotomy is performed depending on the location of the defect. Intravenous antibiotics are administered over the peri-operative period as prophylaxis against infection. Once the defect is identified it is debrided back to a stable rim of normal cartilage. The base of the defect is also debrided down to the subchondral bone, taking care not to make it bleed (figure XV a). A periosteal flap is harvested from the proximal medial tibia and sutured with 5'0 Dexon sutures to the rim of the defect.

The cultured chondrocytes are then injected underneath the periosteal flap into the defect (figure XV b). The knee is then closed in the standard way. In Brittbergs' original study the patients' knee was placed in a small elastic bandage and active movement without weight bearing was initiated 2-3 days post surgery. Weight bearing was introduced gradually with exercises to strengthen the quadriceps mechanism over the 8 week period post surgery.

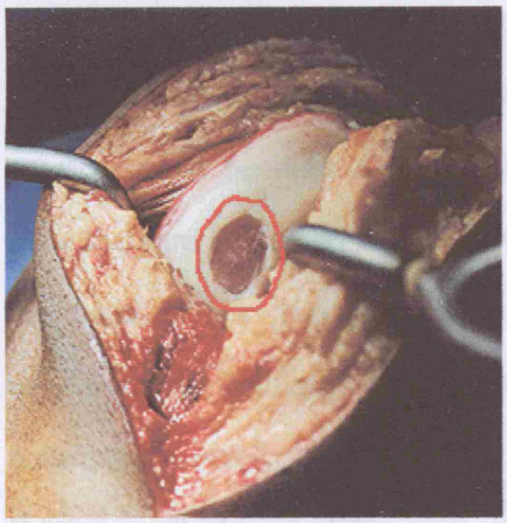

Figure XVa

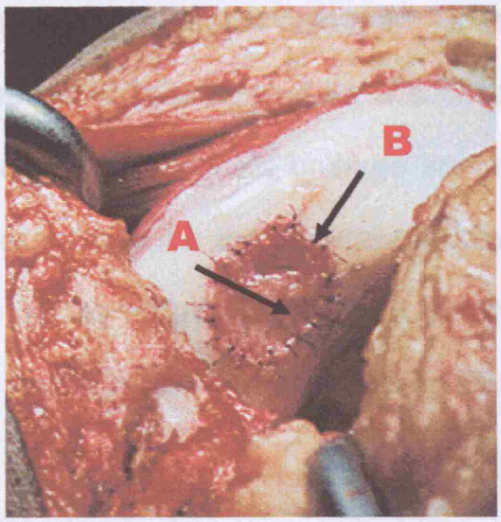

Figure XVb

Figure XV. a. Photograph showing an osteochondral defect over the medial femoral condyle post debridement. **b.** Photograph of defect immediately following an autologous chondrocyte implantation with periosteum cover (A) secured with multiple sutures (B).
(Courtesy of The Center for Orthopaedics & Sports Medicine , 1211 Johnson Ferry Rd., Marietta, G.A.)

Subsequent studies have revealed that up to 50 times the original number of cells can be cultured [153]. Le Baron and Athanasiou [154] performed a study seeding a manufactured scaffold with chondrocytes, they reported that scaffolds with less than 10 million cells/ml resulted in poor cartilage formation. Puelacher et al [155] noted that scaffolds seeded with 20-100 million cells/ml resulted in cartilage formation when implanted subcutaneously into nude mice. However in normal articular cartilage there is only 10,000 cells/mm^2. Possible reasons for the relatively high concentration of cells needed for a successful repair may be because a large number of implanted cells undergo apoptosis once they are implanted into the defect or perhaps it is the physical crowding of the cells that is needed for them to redifferentiate into type II secreting chondrocytes. Brittberg et al [153] in their recent review advocated using $30x10^6$ cells/ml in the clinical setting.

Brittberg [36] classified the patients clinical outcome as excellent (no pain, swelling or locking with strenuous activity), good (mild aching with strenuous activity but no swelling), fair (moderate pain with strenuous activity and occasionally swelling but no locking) or poor (pain at rest, swelling and locking). Of those patients with repairs to condylar defects, 14 of the 16 patients had good or excellent results. When these patients had a second look arthroscopy, the grafts were level with the surrounding articular cartilage and were firm to probing. Biopsies taken of the grafts from the good/excellent group revealed on histological analysis the appearance of hyaline cartilage in 11 of the 15 patients biopsied. Immunostaining for type II collagen in biopsy specimens from 5 patients were positive. In common with other repair techniques the patellar defects did not do so well with only 2 out of 7 patients reporting a good or excellent result. The authors suggested that the poor outcome for patellar

defects maybe due to additional pathology such as abnormal patellofemoral joint mechanics that were not corrected at the time of the procedure.

Encouraged by these results variants of autologous chondrocyte implantation have been tried in approximately 10,000 patients worldwide [153].

In 2002 Peterson and Brittberg et al [72] reported on the long-term durability of autologous chondrocyte implantation. They evaluated 61 patients who had been treated for isolated cartilage defects over the femoral condyle or patella, with a mean follow up of 7.4 years. Defects ranged from 1.3 to 12.0 cm^2. After 2 years 50 of the 61 patients had good or excellent results. When reviewed again at 5-11 years later, 51 of the 61 patients had good or excellent results. These results suggested that long-term symptom relief could be achieved with this technique. In general other techniques that aim to resolve patients symptoms associated with lesions of the articular cartilage are not as durable. Hubbard et al reported 80% success at 1 year following debridement but this reduced to 59% at the 5 year mark [22]. Similarly, defects repaired by fibrocartilage following arthroscopic abrasion arthroplasty tended not to last beyond the 4 year mark [18].

Several hypotheses have been identified to explain the mechanism of cartilage repair in autologous chondrocyte implantation. Minas and Nehrer [122] suggested three possible mechanisms. The first is that the implanted chondrocytes re-populate the area of the defect and synthesize a new cartilage matrix. The periosteal patch acts simply as a watertight seal ensuring the cells stay within the defect. The second mechanism is that growth factors secreted by the periosteum stimulate the cultured chondrocytes to divide. Finally, the third possible explanation is that the implanted cells and periosteum stimulate chondrocytes in the adjacent cartilage, in the subchondral bone or in the

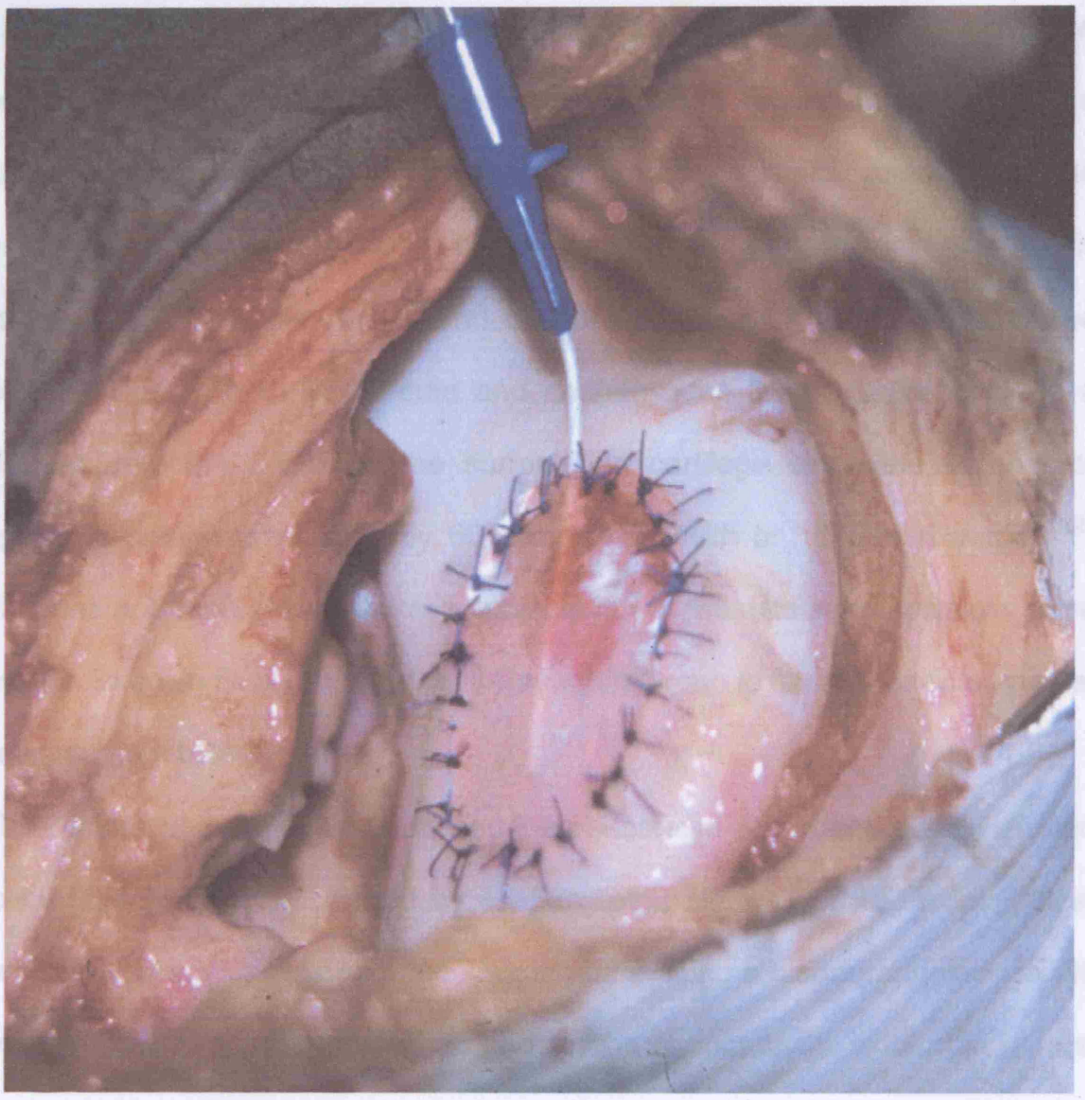

Figure XVI. Photograph of a type I/III collagen membrane secured to the rim of an osteochondral defect located over the medial femoral condyle. A cannula has been introduced through a small opening underneath the membrane so that the suspension of cultured chondrocytes can be injected into the defect. (Courtesy of G. Bentley).

periosteum itself to enter the defect and repair it. The last suggestion can probably be excluded due to the relatively poor results seen in periosteal patch repair of defects in the animal model [156] and in the human subject [127]. Lindahl et al [157] performed a study in which dead periosteum (periosteum which had been snap frozen in liquid nitrogen) was sutured to the rim of the defect and a chondrocyte suspension was injected into the defect underneath the periosteum. Only 1 out of 8 rabbits developed good repair tissue. This suggested that the periosteum and chondrocytes work together to repair the defect. In using both periosteum and chondrocytes there appeared to be a chondroprotective effect on the surrounding cartilage since the number of apoptotic cells was reduced by 60% compared with an untreated defect [158]. This has not been seen in human subjects but the results seen in rabbits have led the Swedish Bone and Cartilage Research Group to favour periosteum over collagen membranes.

This reciprocal arrangement between the periosteum and chondrocytes alluded to by Lindahl is not supported by studies using alternatives to the periosteal flap. Bentley et al [89] reported encouraging data using a biodegradable type I/III collagen membrane (figure XVI) to contain the chondrocytes within the defect. In this study 53 patients had autologous chondrocyte implantation with a type I/III collagen membrane and 5 had a periosteum cover as part of a prospectively randomised study comparing ACI with mosaicplasty. The mean age of the patients was 31.6 years and the mean defect size was 4.66 cm^2. Out of the ACI group, 51 (88%) had a good or excellent result. The mean follow up was 19 months. This confirmed that comparable results could be obtained using a type I/III biodegradable membrane rather than periosteum and favoured the hypothesis that the membrane/periosteum acts purely as a watertight seal.

Concerns have been raised about some aspects of autologous chondrocyte implantation with periosteum or collagen covered techniques [159]. They included the co-morbidity associated with the harvesting of the periosteal flap, the unequal distribution of chondrocytes after injection, with the added possibility of cell leakage beyond the periosteal flap or membrane. Reservations have also been expressed about the placing of multiple sutures in the rim of healthy cartilage to anchor the periosteum or membrane. With these concerns in mind a new technique of implanting the cells into the defect has evolved. The Matrix carried autologous chondrocyte implantation (MACI; Verigen, Leverkusen, Germany) technique uses a similar porcine derived type I/III collagen membrane but is seeded with chondrocytes on one surface. The membrane has special properties that make it a suitable scaffold for supporting the cultured chondrocytes. One surface has a smooth appearance since it has a relatively high density of collagen fibres resulting in a relatively low friction surface and represents the articular cartilage surface. On the reverse the surface appears coarse since it has large gaps between the collagen fibres seen at a microscopic level and is able to harbour cells such as chondrocytes [160]. The chondrocytes are able to anchor themselves to the collagen fibres and form multiple layers on the surface of the membrane.

Implantation of the membrane is preceded by an arthroscopy 4-6 weeks earlier to harvest a sample of cartilage which is enzymatically digested to release the chondrocytes which are then expanded in a monolayer culture. The cultured cells are then seeded onto the membrane at approximately 3 weeks (refer to Genzyme corporation). Similar to the ACI technique the MACI is implanted into the defect via an arthrotomy although there has been some success implanting it arthroscopically [161].

Using the open approach the incision tends to be smaller than that used for the ACI technique. Once the defect has been exposed it is debrided as described for the ACI technique. The membrane is then cut to size and fixed using fibrin glue to the bottom of the defect with the cells facing down (figure XVII). Firm pressure is applied for approximately 30 seconds and the glue is allowed to set for a further 1-2 minutes. The knee is then manipulated to ensure that the graft is stable. If there are concerns about graft stability, Wood et al [162] recommended using 4 tacking sutures at 12, 3, 6 and 9'0' clock. The knee is closed in the standard fashion and the patient is rehabilitated as for the ACI technique.

Previous studies have shown that fibrin glue was detrimental to chondrocytes resulting in apoptosis [163]. Following this study Wood et al [162] performed preclinical studies to assess whether chondrocytes could migrate from a collagen membrane through fibrin glue and anchor themselves to the base of the defect. They demonstrated using an in vitro study that at 2 weeks, cells were seen migrating through the fibrin glue towards the putative subchondral bone.

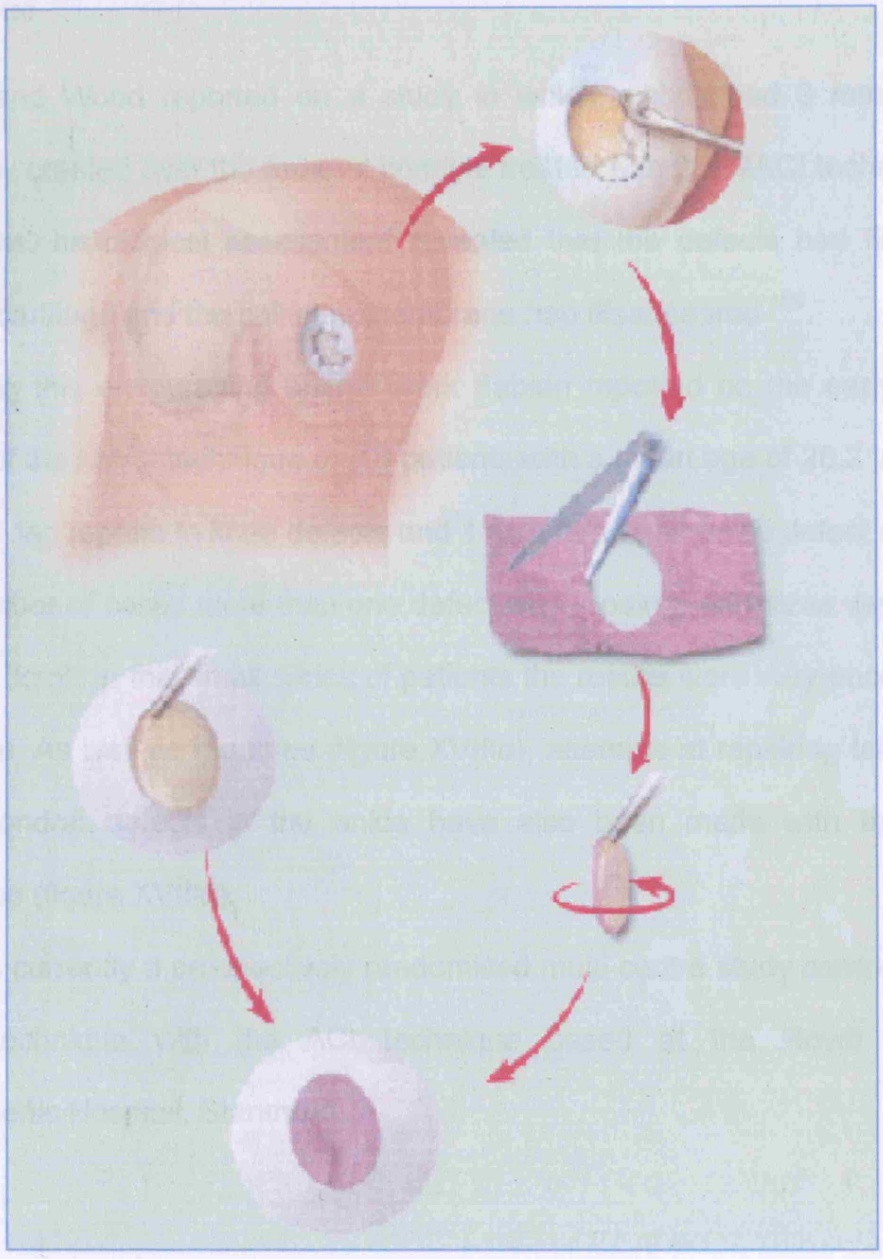

Figure XVII. Schematic diagram illustrating the MACI technique of implanting chondrocytes. Initially the defect is debrided and then the membrane seeded with chondrocytes is cut to size. The membrane is then secured to the base of the defect with fibrin glue. (Courtesy of Verigen UK)

Animal studies in mice have shown that 50% of the membranes disappeared by 21 days following implantation. The extent of membrane degradation appears to be dependent on the degree of crosslinking of the collagens and elastin content [160].

Zheng and Wood reported on a study in which rabbits had 3 mm defects artificially created over the femoral condyle treated with the MACI technique. At 12 weeks, histological assessment revealed that the defects had filled with hyaline cartilage and the collagen membrane had disappeared [160].

Following this encouraging animal work Fabian reported on the early clinical results of the MACI technique on 18 patients with a mean age of 28.2 years. 17 patients had repairs to knee defects and 1 patient had an ankle defect repaired. In a number of cases more than one defect was repaired and sizes varied from $2cm^2$ to $8cm^2$. In this small series of patients the results were very encouraging at 1 year. As well as the knee (figure XVIIIa), attempts at repairing talar dome osteochondral defects in the ankle have also been made with the MACI technique (figure XVIIIb).

There is currently a prospectively randomised multi-centre study comparing the MACI technique with the ACI technique based at the Royal National Orthopaedic Hospital, Stanmore.

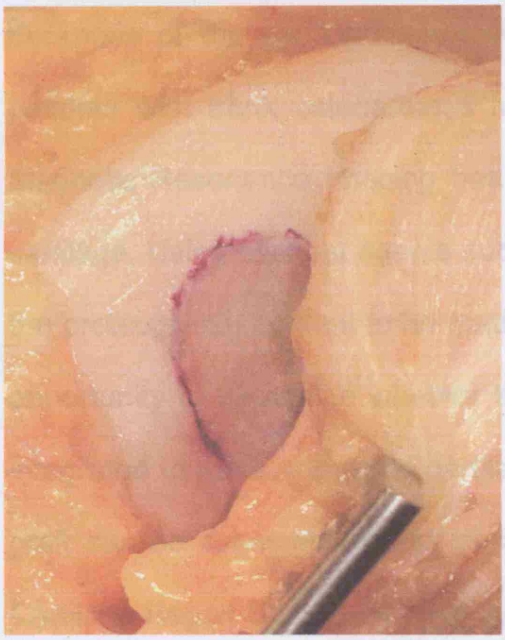

Figure XVIIIa. Osteochondral defect of the medial femoral condyle following a MACI repair.

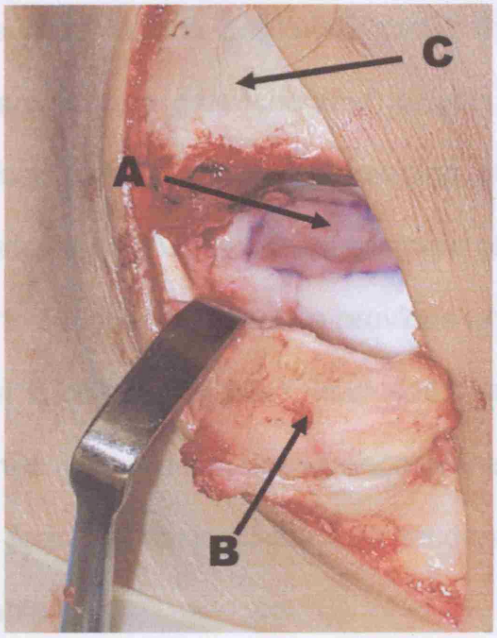

Figure XVIIIb. Osteochondral defect of the talus (A) following a MACI repair. Defect exposed via a medial malleolar osteotomy (B). (C) shows the proximal medial malleolus.

Assessment following autologous chondrocyte implantation

Although improvement in the clinical status following autologous chondrocyte implantation is a very important parameter in assessing the success of a repair, more direct methods can also be used. Traditionally, plain radiographs have been used to assess joint space, which represents an indirect measure of the thickness of the cartilage. However these observations are more useful in patients with frank osteoarthritis rather than discrete osteochondral defects. Magnetic Resonance Imaging has been used extensively for the imaging of cartilage. Using contrast agents such as Gadolinium enables an assessment of the proteoglycan content to be made [164]. Arthroscopic examination provides an opportunity to determine whether the lesion is completely filled, how well it is integrated to the surrounding cartilage and the macroscopic appearance of the graft can be assessed. These parameters form the basis of the International Cartilage Repair Society Grading system (table I).

At the time of the second look check arthroscopy, a biopsy specimen can be taken to assess the repair histologically. Briggs et al [90] reported on 14 implant biopsies taken from patients who had previously had an autologous chondrocyte implantation with a collagen membrane. In the case of 8 patients the defect was sited over the medial femoral condyle, lateral femoral condyle in 4 patients, trochlea in 1 patient and patella in 1 patient. The mean defect size was 2.46 cm^2. Arthroscopic examination in all cases showed that the repair tissue was level with the surrounding cartilage and was firm to probing. Histological examination of 6 biopsies had hyaline cartilage only, 2 had foci of hyaline cartilage within fibrocartilage, 4 had fibrocartilage only and 2 fibrous tissue. Type II collagen was identified in all 8 patients with hyaline cartilage and 3 of the cases that were fibrocartilage. In situ hybridisation revealed that all

samples had the potential to express both type IIa and type IIb collagen. Type IIa collagen is present in a chondroprogenitor cellular phenotype usually found in developing skeletal tissue and type IIb is expressed in mature chondrocytes. It has been suggested that immature chondroprogenitor cells may be essential for the development of repair tissue seen in autologous chondrocyte transplantation. Type X collagen is normally located near the osteochondral junction. Immunostaining for type X and type II collagen revealed that their distribution was similar to that of normal articular cartilage.

This study confirmed that the implantation of cultured chondrocytes into a chondral defect underneath a type II/III collagen membrane could result in a hyaline repair. This would suggest that a periosteum cover is not essential for the development of such a repair.

DOES THE GRAFT FILL THE DEFECT?	
	SCORE
Is it level with surrounding cartilage	4
Is there 75% repair of defect depth	3
Is there 50% repair of defect depth	2
Is there 25% repair of defect depth	1
Or is there 0% repair of defect depth	0

HOW WELL INTEGRATED IS THE GRAFT TO THE BORDER ZONE?	
	SCORE
Complete integration with surrounding cartilage	4
Demarcating border <1mm	3
¾ of graft integrated, ¼ with notable border >1mm width	2
½ of graft integrated with surrounding cartilage, ½ with a notable border >1mm	1
From no contact to ¼ of graft integrated with surrounding cartilage	0

MACROSCOPIC APPEARANCE	
	SCORE
Intact smooth surface	4
Fibrillated surface	3
Small, scattered fissures or cracks	2
Several, small or few but large fissures	1
Total degeneration of grafted area	0

TOTAL SCORE OUT OF 12	

ICRS Grade I	Normal	12
ICRS Grade II	Nearly normal	11-8
ICRS Grade III	Abnormal	7-4
ICRS Grade IV	Severely abnormal	3-1

Table I The International Cartilage Repair Society Grading system for the assessment of chondral and osteochondral defects. [91]

Summary

The treatment of discrete osteochondral defects has proved a challenging clinical problem for a considerable number of years. The inability of cartilage to repair itself has led to the development of a number of novel techniques to manage the symptoms of articular cartilage damage. The early techniques used methods to penetrate the subchondral bone such as drilling and abrasion arthroplasty, which can generate a fibrocartilage repair. Unfortunately this repair tissue lacks the resilience of hyaline cartilage due to important differences in its structure and physiology. As a result long-term studies have not been entirely encouraging for these techniques. Some success has been achieved with osteochondral allografts but these are probably best reserved for large traumatic osteochondral defects and concerns remain regarding disease transmission and immunological rejection.

It has been shown that autologous chondrocyte implantation can result in a durable hyaline repair in the treatment of some focal chondral defects. This can be achieved using cultured chondrocytes together with a membrane to retain the cells and does not require a periosteal flap for the development of a satisfactory repair. With the advent of mesenchymal stem cell technology and the development of biodegradable matrices to act as a conduit for implanting cells, further advances should be forthcoming in this challenging field of Orthopaedic Surgery.

CHAPTER 2:

THEORETICAL JUSTIFICATION FOR THIS WORK

Damage to knee joint cartilage due to various injuries is a common problem with some estimates of more than 10,000 individuals affected each year in the UK (Bentley 2000). From the previous section it can be seen that a number of surgical techniques have been used to address this problem. However a possible problem with traditional techniques such as microfracture or drilling is that they generate fibrocartilage repairs. Although in the short term such repairs can alleviate the patients' symptoms there are concerns as to its durability. It is proposed that with time the fibrocartilage repairs 'degenerates' resulting in a return of the patients' symptoms and progression to osteoarthritis. Techniques such as mosaicplasty tried to address this issue by replacing the exposed subchondral bone with autologous osteochondral plugs. However gaps remain between the plugs which ultimately fill with fibrocartilage and also some of the plugs may delaminate, subside or protrude causing catching and eventual breakdown.

More recently autologous chondrocyte implantation has been proposed as a technique which could enable the repair of a defect with hyaline or hyaline-like cartilage. The advantage of this technique over mosaicplasty is that it does not require the harvesting of osteochondral plugs from the periphery of the knee joint and instead a small sliver of cartilage is taken and then cultured. The ACI technique also enables a more even distribution of chondrocytes over the defect and there are no difficulties of subsidence so that the repair tissue is more likely to restore the normal contours of the articular surface.

The majority of the data to date has been on the periosteum covered ACI and has originated from centres in Gothenburg and the United States. The aim of this study is to assess both clinically and histologically a group of patients over a 4 year period who have undergone the periosteum covered ACI and then to compare this group of patients with other patients who have undergone collagen covered ACI or the MACI technique at a single specialist centre. The results of this study may also help to determine whether periosteum covered ACI is the true gold standard in chondrocyte implantation.

CHAPTER 3:

RESULTS OF THE ACI TECHNIQUE FOR THE TREATMENT OF OSTEOCHONDRAL DEFECTS OF THE KNEE USING A PERIOSTEAL COVER

Introduction

Since the early 1980's Peterson et al have been using autologous articular chondrocytes for the repair of focal articular cartilage defects [36;151;156]. With this technique a small sample of cartilage is taken from the non-weight bearing part of the injured knee. The chondrocytes are then isolated from their extracellular matrix and grown in a monolayer culture. The cultured cells are then implanted into the defect underneath a periosteal patch.

Following Peterson et al's encouraging results with this technique [36;72;91;165] a 4 year review of patients who have had chondral or osteochondral defects repaired with autologous chondrocyte implantation using a periosteal cover was made.

Patients and Methods

The South East Multi-Centre Research Ethics Committee and The Joint Research and Ethical Committee of the Royal National Orthopaedic Hospital Trust gave its approval before commencing this study (G. Bentley 2002 – personal communication).

Patients reviewed at 1 year after operation

A total of 33 patients were reviewed at 1 year with a mean age of 30.58 years (range 15 to 52 years) with symptomatic articular cartilage defects and underwent the ACI technique using a periosteal cover. There were 15 men and 18 women.

The mean defect size was 4.66 cm^2 (range 1 to 9.89 cm^2) with 18 having defects in the right knee and 15 in the left. Of the 33 patients, 8 (24.2%) were on the medial femoral condyle, the patella in 54.6% (12, single facet and 6 multiple facets), the lateral femoral condyle in 3 (9.1%), the trochlea in 3 (9.1%) and 1 patient had multiple defects repaired (table II). The aetiology of the lesions included 13 (39.4%) patients who had post-traumatic defects, 15 (45.5%) who had chondromalacia patellae, 4 (12.1%) had osteochondritis dissecans and 1 patient who had a defect of unknown aetiology, although was most probably post traumatic (table III). Not all patients had a straight forward ACI technique, 3 had a combined ACI and lateral release, 2 had a combined ACI and mosaicplasty to defects to the trochlea, 1 patient had a combined ACI and drilling to the harvest site with a K wire, 1had an ACI and division of a medial plica and 1 patient had a staged anterior cruciate ligament (ACL) reconstruction and ACI technique 6 months later. The mean duration of symptoms was 7.3 years (range 1 to 27 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 1.91 (range 1 to 4).

Patients reviewed at 2 years after operation

A total of 30 patients were reviewed at 2 years with a mean age of 31 years (range 17 to 52 years). There were 13 men and 17 women. The mean defect size was 4.73 cm^2 (range 1 to 9.89 cm^2) with 16 having defects in the right knee and 14 in the left. Of the 30 patients, 6 (20%) were on the medial femoral condyle, the patella in 18 (60%) (12, single facet and 6 multiple facets), the lateral femoral condyle in 3 (10%), the trochlea in 2 (6.67%) and 1 patient had multiple defects repaired (table II). The aetiology of the lesions included 11 (36.67%) patients who had post-

traumatic defects, 15 (50%) patients who had chondromalacia patellae, 3 (10%) had osteochondritis dissecans and 1 patient who had a defect of unknown aetiology (table III). A number of the patients reviewed at 2 years had combined procedures including, 2 patients who had a combined ACI and lateral release, 2 patients who had a combined ACI and mosaicplasty to defects over the trochlea, 2 patients who had an ACI and also required drilling to the harvest site, 1 patient who had a medial plica divided at the time of the ACI and 1 patient who had a staged ACL reconstruction followed by an ACI 6 months later. The mean duration of symptoms was 7.4 years (range 1 to 27 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2 (range 1 to 4).

Patients reviewed at 3 years after operation

A total of 17 patients were reviewed at 3 years with a mean age of 30.5 years (range 20 to 39 years). There were 7 men and 10 women. The mean defect size was 3.99 cm^2 (range 1.5 to 8.75 cm^2) with 9 having defects in the right knee and 8 in the left. Of the 17 patients, 5 (29.4%) were on the medial femoral condyle, the patella in 8 (47%) (7, single facet and 1 multiple facets), the lateral femoral condyle in 2 (11.8%), the trochlea in 1 (5.9%) and 1 patient who had multiple defects repaired (table II). The aetiology of the lesions included 8 (47.1%) patients who had post-traumatic defects, 6 (35.2%) who had chondromalacia patellae, 2 (11.8%) who had osteochondritis dissecans and 1 patient who had a defect of unknown aetiology (table III). A number of patients reviewed at 3 years had combined procedures including 1 who had a combined ACI and mosaicplasty to a defect over the trochlea, 1 patient who had an ACI and drilling to the harvest site with a K wire, 1 patient who had and ACI and lateral release and 1 patient who had a staged ACL

reconstruction followed by an ACI 6 months later. The mean duration of symptoms was 6.9 years (range 1.5 to 23 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 1.88 (range 1 to 4).

Patients reviewed at 4 years after operation

A total of 7 patients were reviewed at 4 years with a mean age of 31.9 years (range 23 to 39 years). There were 5 men and 2 women. The mean defect size was 3.64 cm^2 (range 1.5 to 8.75 cm^2) with 4 having defects in the right knee and 3 in the left. Of the 7 patients, 1 (14.3%) was on the medial femoral condyle, the patella in 4 (57.1%) (all single facet) and the lateral femoral condyle in 2 (28.6%) (table II). The aetiology of the lesions included 4 (57%) patients who had post-traumatic defects and 3 (43%) who had chondromalacia patellae. One patient had a combined ACI and mosaicplasty to a defect over the trochlea and 1 patient who had an ACI and drilling to the harvest site with a K wire. The mean duration of symptoms was 5.4 years (1.6 to 18 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 1.86 (range 1 to 4).

ANATOMICAL DISTRIBUTION	NUMBER OF PATIENTS AT 1 YEAR	NUMBER OF PATIENTS AT 2 YEARS	NUMBER OF PATIENTS AT 3 YEARS	NUMBER OF PATIENTS AT 4 YEARS
Medial Femoral Condyle	8	6	5	1
Lateral Femoral Condyle	3	3	2	2
Patella-single facet	12	12	7	4
Patella-multi facet	6	6	1	
Trochlea	3	2	1	
Multiple defects	1	1	1	
Total	**33**	**30**	**17**	**7**

Table II. Anatomical site of the defects found in 33 patients at 1 year, 30 at 2 years, 17 at 3 years and 7 at 4 years.

AETIOLOGY OF DEFECTS	NUMBER OF PATIENTS AT 1 YEAR	NUMBER OF PATIENTS AT 2 YEARS	NUMBER OF PATIENTS AT 3 YEARS	NUMBER OF PATIENTS AT 4 YEARS
Trauma	13	11	8	4
Osteochondritis dissecans	4	3	2	
Chondromalacia patellae	15	15	6	3
Other	1	1	1	
Total	**33**	**30**	**17**	**7**

Table III. Aetiology of the defects found in 33 patients at 1 year, 30 at 2 years, 17 at 3 years and 7 at 4 years.

The indication for surgery in all cases was pain associated with a chondral or osteochondral defect, other symptoms included swelling, giving way, catching and locking.

Surgical Technique for Autologous Chondrocyte Implantation with a periosteal cover

The procedure was divided into 2 stages as described by Brittberg et al [36] and is summarized here. An arthroscopy was carried out initially. If the defect was suitable for chondrocyte implantation, a full thickness cartilage biopsy of approximately 300-500 mg was harvested from the margin of the trochlea of the damaged knee using a gouge. The specimen was then removed from the knee via one of the arthroscopy portals. The cartilage biopsy was then put into a sterile container and transferred to the laboratory. In the laboratory the specimen was enzymatically digested releasing the chondrocytes, which were then grown in a monolayer culture. The patient was readmitted 3 to 5 weeks following the harvest of cartilage and the second stage of the procedure was performed.

To ensure a bloodless field a tourniquet was applied and a medial or lateral parapatellar arthrotomy was performed depending on the location of the defect. Intravenous antibiotics (1g of flucloxacillin and 1g of amoxycillin) were administered over the peri-operative period as prophylaxis against infection. Once the defect was identified it was debrided back to a stable rim of normal cartilage. The base of the defect was also debrided down to the subchondral bone, taking care not to make it bleed. If bleeding did occur a swab soaked in 1:200,000 adrenaline solution was applied directly to the base of the defect to control it.

To retain the cultured chondrocytes within the defect, a periosteal flap was harvested from the patients' proximal tibia or distal femur. The periosteum was secured to the rim of the defect using multiple 6 '0' vicryl sutures placed 3-4 mm apart. A purple suture material was used so that it could be seen against the white cartilage. The sutures were applied leaving a small 2-3 mm gap between the final two sutures, through which a cannula could be inserted. Attached to this cannula was a syringe containing the cultured chondrocytes in a suspension. A 'water-tight' test was not performed because of concerns that the Hartmann's solution maybe toxic to the cultured chondrocytes. Fibrin glue was applied to the suture line as a seal. The chondrocytes were then injected underneath the periosteal flap into the defect. Enough of the chondrocyte suspension was infiltrated to cause tenting of the flap. Approximately 6 million cells were injected with a range of 5 to 10 million cells depending on the size of the lesion. The small opening through which the chondrocytes had been injected was closed and the entire suture line was re-inforced where necessary with more fibrin glue. After three minutes once the glue had set, the knee was manipulated to ensure that the graft was stable. The knee was closed in layers using non-absorbable sutures.

One patient required reconstruction of the anterior cruciate ligament (ACL), which was performed 6 months prior to the chondrocyte implantation. A hamstring repair was used which was routed through standard tibial and femoral tunnels. Femoral fixation was achieved through a separate lateral incision with the anchoring sutures attached over a biodegradable post. The tibial fixation was secured using a biodegradable screw. Six months later the chondrocyte implantation was performed as described.

There were 2 patients who were considered suitable for a combined ACI and mosaicplasty. Both procedures were performed under the same general anaesthetic. For the mosaicplasty technique, large mosaic plugs 4.5mm in diameter were used when possible to fill the defect. The plugs were placed slightly prominent in order to allow contact with the opposite articular surface during normal movement. This was thought to help with nutrition of the cartilage. The plugs of cartilage were harvested from the margins of the trochlea. Attempts were made to match the slope of the donor articular surface to the contour of the defect. Once the mosaicplasty had been performed the chondrocyte implantation was then undertaken as previously described. At the end of the procedure the joint was moved through a full range of movement to check that both the mosaics and the chondrocyte implantation were stable and did not catch.

Rehabilitation

Following closure of the wound the leg was placed in a compressive Robert Jones bandage that was reinforced with a plaster of Paris backslab. Patients were encouraged to rest overnight with the leg elevated and perform regular foot and ankle exercises. Full weight bearing was encouraged at 24 hours following surgery to stimulate cartilage metabolism. Once the post-operative swelling had diminished, which was usually at 2 to 3 days after surgery the backslab was removed and a light weight fibre glass cylinder cast with the knee in full extension was applied. Once the patients were safe mobilizing with crutches and fully weight bearing, they were discharged. After 10 days the cast was removed and the patients were allowed to continue fully weight bearing with crutches. Patients attended regular physiotherapy sessions at least twice a week for the first two weeks doing graduated active exercises in order to achieve a full range of

movement. At the two week stage if the wound was completely healed, patients were encouraged to perform other activities such as swimming, cycling on an exercise bike without any resistance and rowing exercises. At 6 weeks it was anticipated that the patients would be able to straight leg raise and flex their operated knee to 90°. If patients were making satisfactory progress at the 6 week clinical review they discarded their crutches and continued their exercise programme under the supervision of a Physiotherapist. By 6 months if the patients were making good progress, light jogging was allowed but patients were advised to avoid sporting activities until after the 12 month review and check arthroscopy.

The patients who had an ACL repair as well as a chondrocyte implantation were rehabilitated in the immediate post-operative period on a continuous passive motion machine and were discharged once they achieved 90° of flexion. Further rehabilitation focused on improving the patients' range of movement and muscle strengthening exercises.

Evaluation of Results

Patients were reviewed in the Orthopaedic Clinic at regular intervals in the first year and 6 monthly thereafter. One Observer, who did not perform any of the implantations, independently reviewed the patients. A clinical and functional assessment was made using the modified Cincinnati rating system [166], (table IV) and the Bentley functional rating system [106]. As reported by Bentley et al [89] there was no difference in the results when using either system. The results were graded as excellent (> 80), good (55 to 79), fair 30 to 54) and poor (<30) based on the

modified Cincinnati rating system. Those with an excellent or good result were considered a success whereas those with a fair result were considered unchanged and those with poor results were worse than they were before implantation.

Where possible arthroscopy and biopsy of the grafted area was performed at 1 year from the procedure. In some instances this was not possible because of the inaccessibility of the graft especially in the patellofemoral joint and also patients who declined a further arthroscopy. The repair was assessed using the International Cartilage Repair Society (ICRS) grading system. A 2.5mm biopsy was taken from the centre of the graft using a Jamshidi biopsy needle (see figure XIX) which was angled so that it was perpendicular to the surface. In the case of the patellofemoral joint it was often quite difficult to angle the needle correctly. Care was taken to ensure that some of the subchondral bone was included in the biopsy specimen so that the degree of bonding of the graft to the underlying bone could be assessed. The specimens were all examined by a Pathologist with a special interest in the musculoskeletal system.

Statistical analysis. Statistical comparison of the clinical assessment scores at 1,2,3 and 4 years was by the paired Students T test. Comparisons between the good and excellent group and fair and poor group were made using the unpaired Student T test. A p value of less than 0.05 was considered statistically significant.

PARAMETER	MAXIMUM SCORE
Pain	20
Giving way	20
Swelling	10
Walking ability	10
Stair walking	10
Running	5
Jumping/twisting	5
Overall activity	20
Total	**100**

Table IV. The Modified Cincinnati Rating System (for the sake of clarity this is the abbreviated version, the full version can be found on pages 306-309 in the appendices).

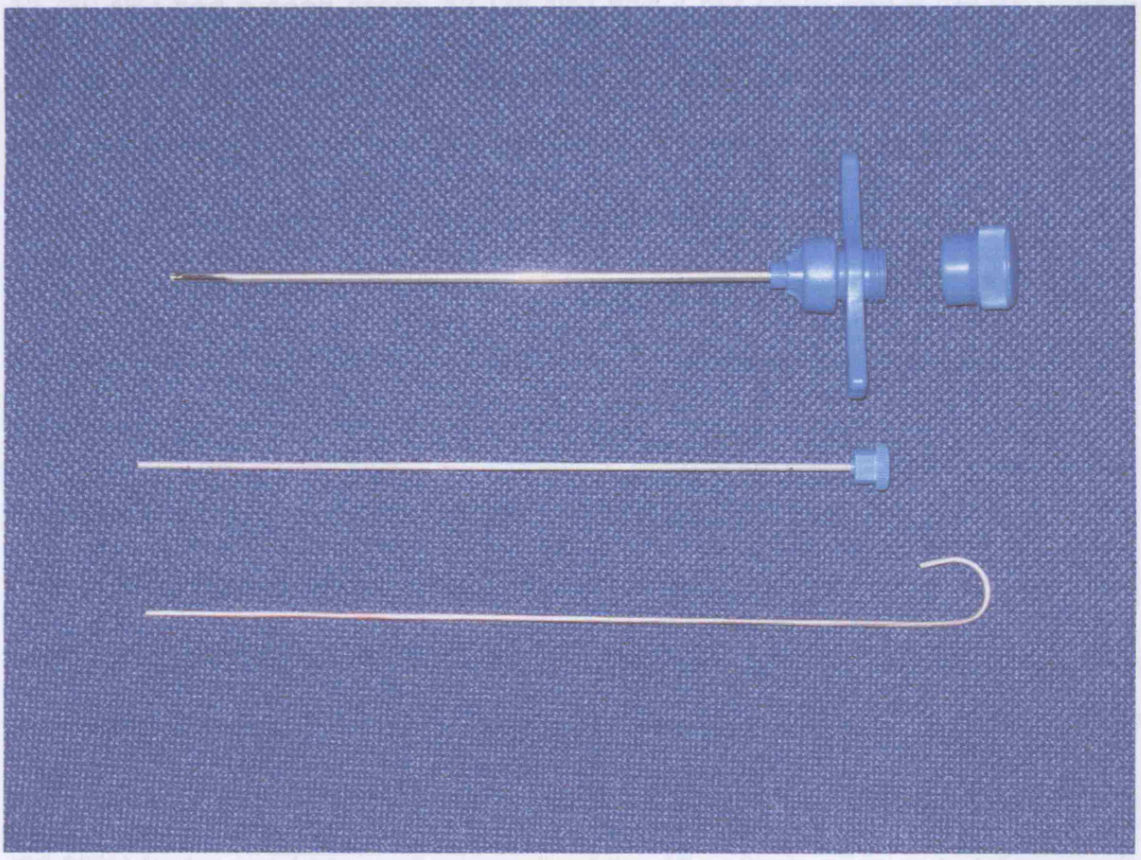

Figure XIX Photograph of a Jamshidi biopsy needle, used to take biopsies from the grafted defects.

Results

Clinical Review

The pre-operative modified Cincinnati rating system scores are shown in table V, 13 (39.4%) had a good score, 12 (36.4%) had a fair score and 8 (24.2%) had a poor score. Those patients with a good score were considered for an ACI, since they complained of considerable pain that was attributed to an articular cartilage defect. All these patients were athletic and functioned at a high level so that they were able to compensate on the remaining parameters of the modified Cincinnati score, which in this situation tends to give a misleading good impression of their symptomatology.

There was a significant improvement in the modified Cincinnati score at 1 year ($p<0.005$) at 2 years ($p<0.005$) and at 3 years ($p<0.005$) (table Va, Vb, Vc). The numbers of patients reviewed at 4 years were too small for statistical analysis (table Vd). Overall, of the 33 patients who were reviewed at 1 year 26 (78.8%) patients had a good or excellent result, of the 30 patients reviewed at 2 years 20 (66.67%) had a good or excellent result, of the 17 patients reviewed at 3 years 11 (64.7%) had a good or excellent result and of the 7 patients reviewed at 4 years 6 (85.7%) patients had a good or excellent result.

The mean modified Cincinnati knee score improved from 46 pre operatively to 68 post operatively at 1 year ($p<0.005$), representing a difference of the means of 22 (95% confidence interval between 13.7 and 29.97, n=33). The mean modified Cincinnati knee score improved from 44 pre operatively to 61 ($p<0.005$) at 2 years, representing a difference of the means of 17 (95% confidence interval between

TOTAL	EXCELLENT	GOOD	FAIR	POOR
33		13	12	8

Table V. Modified Cincinnati scores before ACI-P technique.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
33	9	17	6	1

Table Va.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
30	9	11	7	3

Table Vb.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
17	2	9	4	2

Table Vc.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
7	3	3		1

Table Vd.

Table Va,b,c,d Modified Cincinnati scores at 1 year (table Va), 2 years (table Vb), 3 years (table Vc) and 4 years (table Vd) following ACI-P technique.

9.77 and 24.03, n=30). The mean modified Cincinnati knee score improved from 42 pre operatively to 60 ($p<0.005$) at 3 years, representing a difference of the means of 18 (95% confidence interval between 7.21 and 29.03, n=17). The numbers at 4 years were too small to be statistically significant (n=7).

Factors affecting outcome

It was apparent when reviewing the patients that there seemed to be a difference between those patients who had a good or excellent result and those that had a fair or poor result. Table VI shows the difference between these groups in terms of their age, defect size, duration of symptoms leading up to surgery and number of surgical procedures before implantation.

Although patients in the Good or Excellent group were younger and had smaller defects this did not reach statistical significance.

Making a similar comparison at 2 years between the good/excellent group and the fair/poor group again showed that the patients with a better result were younger and had smaller defects however this did not achieve statistical significance ($p=0.78$ and $p=0.54$ respectively). A similar comparison at 3 years again showed that patients in the good/excellent group were younger (mean age 28.36 years) compared with the fair/poor group mean age 34.3 years and had smaller defects 3.34cm^2 compared with 5.43 cm^2. This time the difference was statistical significant in terms of age ($p=0.05$) and defect size ($p<0.005$). The number of patients reviewed at 4 years was too small for statistical analysis.

	GOOD/ EXCELLENT	FAIR/ POOR	P VALUE
MEAN AGE (YRS)	30.42 (range 15-52)	31.14 (range 17-46)	p=0.84
MEAN DEFECT SIZE (CM^2)	4.59 (range 1.5-9.89)	4.96 (range 1-8.75)	p=0.72
MEAN DURATION OF SYMPTOMS (YRS)	7.8 (range 1-27)	5.42 (range 2-13)	p=0.38
NUMBER OF PREVIOUS PROCEDURES	1.96 (range 1-4)	1.71 (range 1-3)	p=0.58

Table VI. Comparison between the Good/excellent group and the Fair/poor group at 1 year and p values, following the ACI-P technique.

Femoral Condylar Defects

Eleven patients with 8 medial and 3 lateral femoral condylar defects were reviewed at 1 year. The mean age of the patients was 28.1 years (range 15 to 38 years) with a mean defect size of 5.02 cm^2 (range 1.5 to 9 cm^2). The mean duration of symptoms leading up to surgery was 7.5 years (range 1.6 to 15 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 1.9 (range 1 to 4). Nine patients with 6 medial and 3 lateral femoral condylar defects were reviewed at 2 years and 7 patients with 5 medial and 2 lateral femoral condylar defects were reviewed at 3 years. At 4 years, 3 patients with 1 medial and 2 lateral condylar defects were reviewed. Using the modified Cincinnati Rating System, of those patients who had repairs to defects over the medial femoral condyle, 7 out of 8 reported good or excellent results at 1 year, 3 out of 6 at 2 years, 2 out of 5 at 3 years and 1 patient at 4 years reported a poor result. Of the patients who had repairs to defects over the lateral femoral condyle 3 out of 3 reported a good or excellent result at 1 year, 3 out of 3 at 2 years, 2 out of 2 at 3 years and 2 out of 2 at 4 years.

TIME OF REVIEW	CLINICAL OUTCOME	MEDIAL FEMORAL CONDYLE	LATERAL FEMORAL CONDYLE
1 YEAR	Excellent	2	2
	Good	5	1
	Fair	1	
	Poor		
	Total	**8**	**3**
2 YEARS	Excellent		2
	Good	3	1
	Fair	2	
	Poor	1	
	Total	**6**	**3**
3 YEARS	Excellent		1
	Good	2	1
	Fair	2	
	Poor	1	
	Total	**5**	**2**
4 YEARS	Excellent		1
	Good		1
	Fair		
	Poor	1	
	Total	**1**	**2**

Table VII. Clinical results at 1,2,3 and 4 years for patients who had an ACI-P for chondral and osteochondral defects over the medial and lateral femoral condyle of the knee.

Patellar defects

Eighteen patients with 13 single facet and 5 with multi-facet defects were reviewed at 1 year. The mean age of the patients was 29.94 years (17 to 46 years) with a mean defect size of 4.53 cm^2 (range 1 to 8.75 cm^2). The mean duration of symptoms leading up to surgery was 5.75 years (range 1 to 18 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 1.78 (range 1 to 4). Eightteen patients with 12 single facet and 6 with multi-facet defects were reviewed at 2 years and 8 patients with 7 single facet and 1 with multi-facet defects were reviewed at 3 years. At 4 years, 4 patients with single facet defects were reviewed.

Using the modified Cincinnati Rating system, of those patients who had repairs to defects over a single facet of the patella, 8 out of a total of 13 patients (61.5%) reported good or excellent results at 1 year, 7 out of 12 (58.3%) at 2 years, 5 out of 7 (71.4%) at 3 years and 4 out of 4 at 4 years. Of those patients who had repairs to defects over both facets of the patella, 6 out of 6 reported good or excellent results at 1 year, 5 out of 6 (71.4%) at 2 years and 1 out of 1 at 3 years.

TIME OF REVIEW	CLINICAL OUTCOME	SINGLE FACET PATELLAR DEFECT	MULTI-FACET PATELLAR DEFECT
1 YEAR	Excellent	3	2
	Good	5	4
	Fair	4	
	Poor	1	
	Total	**13**	**6**
2 YEARS	Excellent	3	3
	Good	4	2
	Fair	2	1
	Poor	3	
	Total	**12**	**6**
3 YEARS	Excellent	1	
	Good	4	1
	Fair	2	
	Poor		
	Total	**7**	**1**
4 YEARS	Excellent	2	
	Good	2	
	Fair		
	Poor		
	Total	**4**	

Table VIII. Clinical results at 1,2,3 and 4 years for patients who had an ACI-P for chondral and osteochondral defects over the patella (single and multi-facet).

Traumatic defects

Of the 33 patients reviewed at 1 year, 13 (39.4%) had defects of traumatic origin. The mean age of the patients was 34.5 years (range 26 to 52 years) with a mean defect size of 4.53 cm^2 (range 1.5 to 9.89 cm^2). The mean duration of symptoms leading up to surgery was 8.5 years (range 1.5 to 27 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2 (range 1 to 4). Eleven patients were reviewed at 2 years, 7 at 3 years and 4 at 4 years. Using the modified Cincinnati rating system, of those patients who were reviewed at 1 year, 11 out of a total of 13 (84.6%) patients reported good or excellent results, 8 out of 11 (73%) at 2 years, 4 out of 7 (57.1%) at 3 years and 3 out of 4 (75%) at 4 years (table IX).

TIME OF REVIEW	CLINICAL OUTCOME	TRAUMATIC DEFECTS
1 YEAR	Excellent	4
	Good	7
	Fair	2
	Poor	
	Total	**13**
2 YEARS	Excellent	4
	Good	4
	Fair	3
	Poor	
	Total	**11**
3 YEARS	Excellent	1
	Good	3
	Fair	2
	Poor	1
	Total	**7**
4 YEARS	Excellent	1
	Good	2
	Fair	
	Poor	1
	Total	**4**

Table IX. Clinical results at 1,2,3 and 4 years for patients who had defects of traumatic origin, following ACI-P.

Chondromalacia Patellae

Of the 33 patients reviewed at 1 year, 15 (45.5%) had defects attributed to chondromalacia patellae. The mean age of the patients was 29.3 years (range 17 to 46 years) with a mean defect size of 4.25 cm^2 (range 1 to 8.75 cm^2). The mean duration of symptoms leading up to surgery was 6 years (range 1 to 18 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 1.73 (range 1 to 4). Fourteen patients were reviewed at 2 years, 6 at 3 years and 3 at 4 years.

Using the modified Cincinnati rating system, of those patients who were reviewed at 1 year, 10 out of a total of 15 (66.7%) patents reported good or excellent results, 10 out of 15 (66.7%) at 2 years, 5 out of 6 (83.3%) at 3 years and 3 out of 3 at 4 years (table X).

TIME OF REVIEW	CLINICAL OUTCOME	CHONDROMALACIA PATELLAE
1 YEAR	Excellent	3
	Good	7
	Fair	4
	Poor	1
	Total	**15**
2 YEARS	Excellent	5
	Good	5
	Fair	3
	Poor	2
	Total	**15**
3 YEARS	Excellent	1
	Good	4
	Fair	1
	Poor	
	Total	**6**
4 YEARS	Excellent	2
	Good	1
	Fair	
	Poor	
	Total	**3**

Table X. Clinical results at 1,2,3 and 4 years for patients who had defects attributed to chondromalacia patellae, following ACI-P.

The numbers of patients with trochlea and multiple defects and whose defects were attributed to osteochondritis dissecans were too small for useful analysis.

Arthroscopic review

A repeat arthroscopy at 1 year following the implantation revealed ICRS grades of 1 or 2 in 24 of 30 patients (80%). The arthroscopy of 1 patient did not show any evidence of the graft and scored an ICRS of 4 (table XI). Nine arthroscopies were carried out at the 2 year review, which revealed ICRS grades of 1 or 2 in 5 of 9 patients (55.6%). In the case of 1 patient there was no evidence of the graft and scored 4 on the ICRS grading system. Further review arthroscopies were not carried out unless there was a clinical indication.

Of the 13 biopsies taken at the time of the 1 year check arthroscopy, 5 were from the medial femoral condyle, 1 from the lateral femoral condyle and 7 from the patella. Of the 3 biopsies taken at the 2 year check arthroscopy, 2 were from the medial femoral condyle and 1 from the lateral femoral condyle.

Hyaline cartilage of normal appearance was found in 2 of the biopsies taken at 1 year, consisting of cells located within a lacuna enveloped within a matrix that stained strongly for type II collagen using Safranin O. Of the remaining biopsies taken at 1 year, 4 showed evidence of mixed hyaline and fibrocartilage and 7 showed evidence of fibrocartilage.

Of those biopsied at 2 years, 1 showed evidence of hyaline cartilage and 2 mixed hyaline and fibrocartilage.

ICRS GRADE	NUMBER (%)	
	1 YEAR	2 YEARS
1, Excellent	3	
2, Good	21	5
3, Fair	5	3
4, Poor	1	1
Total	30	9

Table XI. Arthroscopic results at 1 and 2 years, following ACI-P.

One of the grafts biopsied at 1 year showed a mixed picture of hyaline and fibrocartilage however the same graft revealed hyaline cartilage alone when biopsied at 2 years. This may suggest that the grafts can take up to 2 years to fully mature as suggested previously by Bentley [89] and Peterson [91].

Complications

Within the first year following implantation there was 1 major complication, 11 intermediate and 9 minor complications. Within the 2nd year of implantation there was 1 major complication, 1 intermediate and 1 minor complication. Within the 3rd year there were no major complications and 2 intermediate complications and there were no complications within the 4th year from surgery (table XII).

Complications encountered within the 1st year included one patient whose graft failed. The intermediate complications encountered within the first year of the implantation were attributed to hypertrophy of the graft with 11 patients requiring shaving of the graft at the 1 year check arthroscopy and 2 further patients who required an arthroscopy before the 1 year review. Two patients required further shaving of the grafts 6 months after the first shave for graft hypertrophy. Four patients were slow to mobilise in the immediate post operative period and required a manipulation under anaesthetic. One patient required removal of a large fibrous plica at the 1 year check arthroscopy. Of the 4 patients who required an unplanned arthroscopy within the first year 2 were for graft hypertrophy, 1 for ongoing pain and 1 for division of adhesions. At 2 years, there was 1 episode of graft failure after the patient had a fall and 4 patients required shaving of their grafts, which had hypertrophied. One patient was referred to the pain team for ongoing pain.

At 3 years there were 2 patients who required an arthroscopy for graft overgrowth which were shaved.

There were no complications at 4 years.

COMPLICATION	NUMBER
MAJOR	
Graft failure	1 at 1 year 1 at 2 years
INTERMEDIATE	
Graft hypertrophy	11 at 1 year 1 at 2 years 2 at 3 years
MINOR	
Superficial wound infection	1 at 1 year
Slow to mobilise requiring a manipulation under anaesthetic	4 at 1 year
Unplanned arthroscopy	4 at 1 year 1 at 2 years

Table XII. Complications following ACI with a periosteal cover.

Discussion

Autologous chondrocyte implantation with a periosteal cover was first advocated by Peterson et al [151], since October 1987 they have used this technique in approximately 1200 patients [153]. Worldwide, Brittberg et al [153] estimate that variants of autologous chondrocyte implantation have been performed in approximately 10,000 patients.

Brittberg et al have achieved considerable success in the treatment of chondral and osteochondral defects of the knee with this technique. In a clinical evaluation of 244 patients followed for 2 to 10 years the percentage of good to excellent results was high (84% to 90%) for single condylar lesions but was lower (mean 74%) for patients with other types of lesions [153].

The results of our study are encouraging with 78.8% of patients reporting good or excellent results at 1 year, 66.67% at 2 years, 64.7% at 3 years and 85.7% at 4 years.

The findings at the 1 year check arthroscopy revealed that 80% of those who were arthroscoped had repairs that were good or excellent based on the ICRS grading system. At 1 year 1 graft had failed, which was located over the medial facet of the patellar. At 2 years a further graft failed which again was located over the retropatellar surface, however immediately preceding the arthroscopy the patient had a significant fall and the failure was put down to delamination of the graft secondary to trauma. Although both failures occurred in patients with defects over the patella this was not typical of the group as a whole, with 72% of patients at 1 year reporting good or excellent results, 66.67% at 2 years, 75% at 3 years and 100% at 4 years.

A number of factors were identified that appeared to influence the outcome of the repair. A comparison between the good/excellent group and fair/poor at 1, 2 and 3 years revealed that patients who were younger and had smaller defects did better. However, the differences between age and defect size only reached statistical significance at the 3 year review. Other factors that may influence the clinical outcome were also assessed, including duration of symptoms leading up to surgery and number of surgical procedures before the implantation but there were no significant differences when the good/excellent group and the fair/poor group were compared.

Defects repaired in this study were larger than those repaired in other studies. The mean defect size of the femoral condyle lesions in Peterson et al's [72] recent long-term durability study was 3.4 cm^2 compared with 5.02 cm^2 in this study. In Minas' study the simple defects that he repaired had a mean size of 4.3cm^2. As suggested from the results discussed above defect size has an impact on the clinical outcome following autologous chondrocyte implantation. This may explain why our results (50% good/excellent at 2 years) are not as good as the Swedish experience [72] (89% at 2 years). However, it is difficult to make a direct comparison since it is not clear which scoring system Peterson et al use to arrive at their final figure.

The patients who were part of the Swedish groups' study [72] had a shorter duration of symptoms (3.4 years) compared to our patients (7.3 years). This may explain why the defects in our study were larger since patients have had them for longer. The delay in patients receiving treatment may also have a deleterious psychological effect that may adversely affect the clinical outcome, however this has not been quantified.

We found no evidence to support the argument that the placing of multiple sutures into the surrounding articular cartilage at the margin of the defect results in damage to the cartilage. At the check arthroscopies at 1 and 2 years the articular cartilage adjacent to the graft was intact and appeared healthy.

Repairs to defects that are notoriously difficult to repair such as the lateral femoral condyle did very well. Although only 3 patients were reviewed at 1 and 2 years, all achieved good/excellent results. At 3 and 4 years, 2 patients were reviewed and both achieved good and excellent results at each review.

Patients with traumatic defects did better than those with chondromalacia patellae. At 1 year 84.6% of patients with traumatic defects had good or excellent results compared with 66.6% for those with chondromalacia patellae. However, the site of the defect may also explain the difference between these 2 groups as well as the pathophysiology of the defects.

A review of the histology at 1 and 2 years following the chondrocyte implantation confirmed Peterson et l's [72] findings that this technique can result in a hyaline cartilage repair. Two out of 13 biopsies showed hyaline cartilage alone and 4 showed a mixture of hyaline and fibrocartilage. At 2 years 1 biopsy showed evidence of hyaline cartilage and 2 showed mixed hyaline and fibrocartilage.

Of concern was the high incidence of graft hypertrophy requiring shaving at arthroscopy. At 1 year 11 (33.3%) patients required shaving of hypertrophied grafts but this did not include those patients who required arthroscopies prior to the 1 year check. In total 2 patients required an unplanned arthroscopy within the 1st year for graft hypertrophy and another 2 required a further arthroscopy after the

graft re-hypertrophied. The highest incidence of graft hypertrophy was in the 1st year, with only 4 patients requiring surgical intervention at the 2 year stage.

Some have argued that the periosteum works with the chondrocytes to repair the defect [157]. However, this conclusion was drawn from animal studies and such a relationship has never been demonstrated in human subjects. A prospective randomised study undertaken at this institution comparing ACI using a type I/III collagen cover with ACI using a periosteal cover has shown no difference based on the clinical outcome at 2 years and on arthroscopic assessment (see Chapter 5). Other concerns of this technique include the co-morbidity associated with the longer incision needed for the harvesting of the periosteal flap [89].

In summary, this study has shown that the results in terms of clinical outcome following the repair of chondral and osteochondral defects with ACI using a periosteal cover are encouraging over a 4 year follow-up. However, from this study the rate of graft hypertrophy following this technique requiring an arthroscopy and shaving of the graft is unacceptably high. At the Royal National Orthopaedic Hospital the periosteal cover has been abandoned in favour of the manufactured type I/III collagen cover which can also give a satisfactory repair but with a much lower incidence of graft hypertrophy [89;90] (see Chapter 4).

CHAPTER 4:

RESULTS OF THE ACI TECHNIQUE FOR THE TREATMENT OF OSTEOCHONDRAL DEFECTS OF THE KNEE USING A PORCINE MEMBRANE

Introduction

In their original technique Brittberg et al [36] used a periosteal cover to contain the chondrocytes within the defect (previous chapter). The use of a periosteal cover has brought into question whether it acts simply as a watertight seal or whether it releases factors essential to the development of a hyaline cartilage repair. The extra surgical exposure required to remove a piece of tibial periosteum may cause morbidity and pain to the patient which is also a disadvantage. Following the encouraging clinical results by Bentley et al [89] and the histological results by Briggs et al [90] using a type I/III collagen membrane as apposed to a periosteal cover, a group of patients who had this technique were reviewed over a 4 year period.

Patients and Methods

The South East Multi-Centre Research Ethics Committee and The Joint Research and Ethical Committee of the Royal National Orthopaedic Hospital Trust gave its approval before commencing this study (G. Bentley 2002 – personal communication).

Patients reviewed at 1 year after operation

A total of 130 patients were reviewed at 1 year with a mean age of 32 years (range 14 to 54 years) with symptomatic articular cartilage defects and underwent the ACI technique using a type I/III collagen membrane. There were 70 men and 60 women. The mean defect size was 4.82 cm^2 (range 1-12.5cm^2) with 68 having defects in the right knee and 62 in the left. Of the 130 patients, 52 (40%) were on the medial femoral condyle, the patella in 39 (30%) (27, single facet and 12 multiple facets), the lateral femoral condyle in 19 (15%), the trochlea in 7 (5%) and 13 (10%) patients had multiple defects repaired (table XIII). The aetiology of the lesions included 52 (40%) patients who had post traumatic defects, 23 (17.7%) patients who had chondromalacia patellae, 18 (13.8%) had osteochondritis dissecans, 17 (13.1%) who had previous cartilage resurfacing techniques which had failed, 1 (0.8%) patient had evidence of early osteoarthritis and 19 (14.6%) patients who had defects of unknown aetiology, although they were most probably post traumatic (table XIV). Not all patients had a straightforward ACI technique, 2 had a combined ACI and anterior cruciate ligament reconstruction, 2 had a combined ACI and mosaicplasty to a defect over the trochlea groove, 7 had a combined ACI and drilling to defects not suitable for chondrocyte implantation, 3 had combined ACI and lateral release, 1 patient had combined ACI, mosaicplasty, patella realignment and drilling to the harvest site and 1 patient had a large osteophyte removed at the time of the chondrocyte implantation. The mean duration of symptoms was 7.67 years (range 1 to 25 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.19 (range 1 to 6).

Patients reviewed at 2 years after operation

A total of 82 patients were reviewed at 2 years with a mean age of 30.7 years (range 14 to 54 years). There were 43 men and 39 women. The mean defect size was 4.71 cm^2 (range 1 to 12.25cm^2) with 46 having defects in the right knee and 36 in the left. Of the 82 patients, 32 (16%) were on the medial femoral condyle, the patella in 24 (29%) (18, single facet and 6 multiple facets), the lateral femoral condyle in 13 (16%), the trochlea in 6 (7%) and 7 (9%) patients who had multiple defects repaired (table XIII). The aetiology of the lesions included 37 (45%) patients who had post traumatic defects, 12 (15%) patients who had chondromalacia patellae, 11 (13%) had osteochondritis dissecans, 9 (11%) who had previous cartilage resurfacing techniques which had failed, 1 (1%) patient had evidence of early osteoarthritis and 12 (15%) patients who had defects of unknown aetiology (table XIV). A number of patients reviewed at 2 years had combined procedures including, 2 who had a combined ACI and mosaicplasty to a defect over the trochlea groove, 4 who had a combined ACI and drilling to defects not suitable for chondrocyte implantation, 1 who had a combined ACI and lateral release and 1 patient had a combined ACI, mosaicplasty, patella realignment and drilling to the harvest site. The mean duration of symptoms was 7.08 years (range 1 to 23 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.21(range 1 to 5).

Patients reviewed at 3 years after operation

A total of 41 patients were reviewed at 3 years with a mean age of 30.76 years (range 17 to 49 years). There were 21 men and 20 women. The mean defect size was 4.03 cm^2 (range 1 to 12cm^2) with 46 having defects in the right knee and 36 in

the left. Of the 41 patients, 14 (34%) were on the medial femoral condyle, the patella in 13 (31%) (12, single facet and 1 multiple facets), the lateral femoral condyle in 8 (20%), the trochlea in 4 (10%) and 2 (5%) patients who had multiple defects repaired (table XIII). The aetiology of the lesions included 19 (46%) patients who had post traumatic defects, 7 (17%) patients who had chondromalacia patellae, 6 (15%) had osteochondritis dissecans, 3 (7%) who had previous cartilage resurfacing techniques which had failed and 6 (15%) patients who had defects of unknown aetiology (table XIV). A number of patients reviewed at 3 years had combined procedures including, 1 which had a combined ACI and mosaicplasty, 2 who had a combined ACI and drilling of defects not suitable for chondrocyte implantation and 1 patient had a combined ACI, mosaicplasty, patellar realignment and drilling of the harvest site. The mean duration of symptoms was 6.72 years (range 1 to 23 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.18 (range 1 to 5).

Patients reviewed at 4 years after operation

A total of 16 patients were reviewed at 4 years with a mean age of 32.44 years (range 19 to 49 years). There were 7 men and 9 women. The mean defect size was 3.59 cm^2 (range 1.5 to 6 cm^2) with 8 having defects in the right knee and 8 in the left. Of the 16 patients, 5 (31.25%) were on the medial femoral condyle, the patella in 5 (31.25%) (4, single facet and 1 multiple facets), the lateral femoral condyle in 5 (31.25%) and 1 (6.25%) patient who had multiple defects repaired (table XIII). The aetiology of the lesions included 8 (50%) patients who had post traumatic defects, 2 (12.5%) patients who had chondromalacia patellae, 3 (18.75%) had osteochondritis dissecans and 3 (18.75%) patients who had defects

of unknown aetiology (table XIV). One patient had a combined ACI, mosaicplasty, patellar realignment and drilling to the harvest site. The mean duration of symptoms was 5.85 years (range 1 to 18 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.13 (range 1 to 4).

ANATOMICAL DISTRIBUTION	NUMBER OF PATIENTS AT 1 YEAR	NUMBER OF PATIENTS AT 2 YEARS	NUMBER OF PATIENTS AT 3 YEARS	NUMBER OF PATIENTS AT 4 YEARS
Medial Femoral Condyle	52 *(40%)*	32 *(39%)*	14 *(34%)*	5 *(31.25%)*
Lateral Femoral Condyle	19 *(15%)*	13 *(16%)*	8 *(20%)*	5 *(31.25%)*
Patella-single facet	27 *(21%)*	18 *(22%)*	12 *(29%)*	4 *(25%)*
Patella-multi facet	12 *(9%)*	6 *(7%)*	1 *(2%)*	1 *(6.25%)*
Trochlea	7 *(5%)*	6 *(7%)*	4 *(10%)*	0
Multiple defects	13 *(10%)*	7 *(9%)*	2 *(5%)*	1 *(6.25%)*
Total	**130** ***(100%)***	**82** ***(100%)***	**41** ***(100%)***	**16** ***(100%)***

Table XIII. Anatomical site of the defects found in 130 patients at 1 year, 82 at 2 years, 41 at 3 years and 16 at 4 years, by number and *percentage.*

AETIOLOGY OF DEFECTS	NUMBER OF PATIENTS AT 1 YEAR	NUMBER OF PATIENTS AT 2 YEARS	NUMBER OF PATIENTS AT 3 YEARS	NUMBER OF PATIENTS AT 4 YEARS
Trauma	52 *(40%)*	37 *(45%)*	19 *(46%)*	8 *(50%)*
Osteochondritis dissecans	18 *(13.8%)*	11 *(13%)*	6 *(15%)*	3 *(18.75%)*
Chondromalacia patellae	23 *(17.7%)*	12 *(15%)*	7 *(17%)*	2 *(12.5%)*
Previously failed cartilage resurfacing technique	17 *(13.1%)*	9 *(11%)*	3 *(7%)*	
Early osteoarthritis	1 *(0.8%)*	1 *(1%)*		
Other	19 *(14.6%)*	12 *(15%)*	6 *(15%)*	3 *(18.75%)*
Total	**130** ***(100%)***	**82** ***(100%)***	**41** ***(100%)***	**16** ***(100%)***

Table XIV. Aetiology of the defects found in 130 patients at 1 year, 82 at 2 years, 41 at 3 years and 16 at 4 years, by number and *percentage*

The indication for surgery in all cases was pain associated with a chondral or osteochondral defect, other symptoms included swelling, giving way, catching and locking.

Surgical Technique

The procedure was divided into 2 stages as previously described for the ACI-P technique (pages 106-108). The ACI-C technique differed in that instead of harvesting periosteum from the distal femur or from the proximal tibia a type I/III collagen membrane was cut to size and used to retain the chondrocytes within the defect. The membrane was secured to the rim of the defect using multiple 6 '0' vicryl sutures placed 3-4 mm apart and the edges of the defect were sealed with fibrin glue as before (figure XX).

Two patients required reconstruction of the anterior cruciate ligament (ACL), which was performed before implantation during the same operative procedure. In all cases a hamstring repair was used which was routed through standard tibial and femoral tunnels. Femoral fixation was achieved through a separate lateral incision with the anchoring sutures attached over a biodegradable post. The tibial fixation was secured using a biodegradable screw. Under the same general anaesthetic the ACI procedure was performed as described.

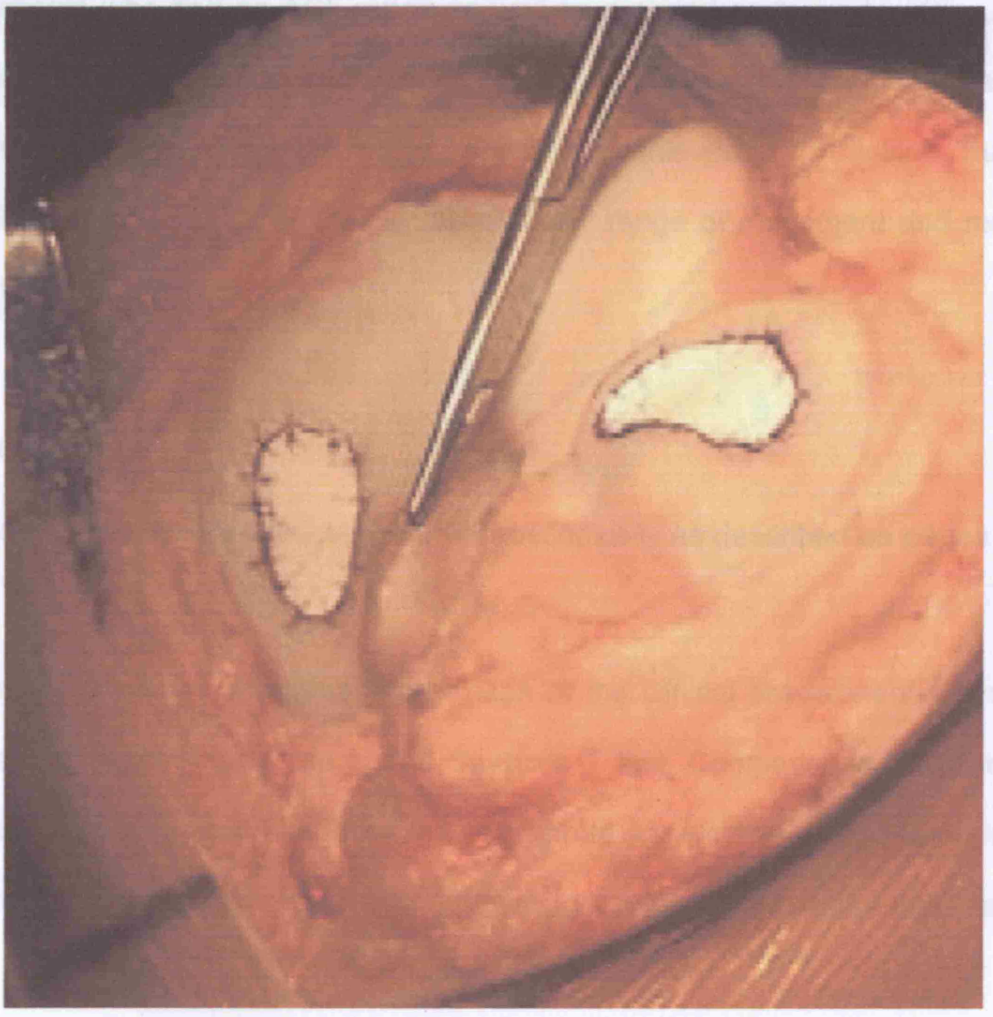

Figure XX. Photograph showing 2 defects repaired with the ACI (collagen covered) technique. One defect is located over the patella and the other over the medial femoral condyle.

Rehabilitation

Rehabilitation for patients following the ACI-C technique was the same as previously described for the ACI-P technique (pages 108-109).

The patients who had an ACL repair as well as a chondrocyte implantation were rehabilitated in the immediate post-operative period on a continuous passive motion machine and were discharged once they achieved 90° of flexion. Further rehabilitation focused on improving the patients' range of movement and muscle strengthening exercises.

Evaluation

Patients were evaluated clinically and arthroscopically as described on pages 109-111.

Statistical analysis. Statistical comparison of the clinical assessment scores at 1,2,3 and 4 years was by the paired Students T test. Comparisons between the good and excellent group and fair and poor group were made using the unpaired Student T test. A p value of less than 0.05 was considered statistically significant.

Results

Clinical Review

The pre-operative modified Cincinnati rating system scores are shown in table XV, 32 (24.6%) had a good score, 57 (43.8%) had a fair score and 41 (31.5%) had a poor score. Those patients with a good score were considered for an ACI, since they complained of considerable pain that was attributed to an articular cartilage defect. All these patients were athletic and functioned at a high level so that they were able to compensate on the remaining parameters of the modified Cincinnati score, which in this situation tends to give a misleading good impression of their symptomatology.

There was a significant improvement in the modified Cincinnati score at 1 year ($p<0.005$) at 2 years ($p< 0.005$), at 3 years ($p<0.005$) and 4 years ($p<0.005$) following surgery. Overall, of the 130 patients who were reviewed at 1 year 81 (62%) patients had a good or excellent result (table XVa), of the 82 patients reviewed at 2 years 48 (59%) had a good or excellent result (table XVb), of the 41 patients reviewed at 3 years (59%) had a good or excellent result (table XVc) and of the 16 patients reviewed at 4 years 9 (56%) patients had a good or excellent result (table XVd).

It became evident during the course of the study that the results for years 1,2 and 3 were adversely affected by a group of patients who had an ACI following a previous cartilage resurfacing technique, such as mosaicplasty or the matrix support prosthesis. Excluding this group the results were as follows; at 1 year, 77 (68%) out of 113 patients reported good or excellent results, at 2 years 47 (64%) out of 73 patients and at 3 years 23 (61%) out of 38 patients.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
130 *(100%)*		32 *(24.6%)*	57 *(43.8%)*	41 *(31.5%)*

Table XV. Modified Cincinnati scores before ACI-C, numbers and *percentages.*

TOTAL	EXCELLENT	GOOD	FAIR	POOR
130 *(100%)*	34 *(26%)*	47 *(36%)*	27 *(21%)*	22 *(17%)*

Table XVa.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
82 *(100%)*	27 *(33%)*	21 *(26%)*	20 *(24%)*	14 *(17%)*

Table XVb.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
41 *(100%)*	11 *(26.8%)*	13 *(31.7%)*	13 *(31.7%)*	4 *(9.8%)*

Table XVc.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
16 *(100%)*	4 *(25%)*	5 *(31.3%)*	5 *(31.3%)*	2 *(12.5%)*

Table XVd.

Table XVa,b,c,d Modified Cincinnati scores at 1 year following ACI-C (table XVa), 2 years (table XVb), 3 years (table XVc) and 4 years (table XVd) by numbers and *percentages.*

The mean modified Cincinnati knee score improved from 42 pre operatively to 60 post operatively at 1 year ($p<0.05$), representing a difference of the means of 18 (95% confidence interval between 14.09 and 22.12, n=130). The mean modified Cincinnati knee score improved from 41 pre operatively to 62 ($p<0.05$) at 2 years, representing a difference of the means of 21 (95% confidence interval between 15.80 and 26.0, n=82). The mean modified Cincinnati knee score improved from 40 pre operatively to 61 ($p<0.05$) at 3 years, representing a difference of the means of 21 (95% confidence interval between 14.17 and 28.90, n=41). The mean modified Cincinnati knee score improved from 44 pre operatively to 61 ($p<0.05$) at 4 years, representing a difference of the means of 17 (95% confidence interval between 9.0 and 24.25, n=16).

Factors affecting outcome

It was apparent when reviewing the patients that there seemed to be a difference between those patients who had a good or excellent result and those that had a fair or poor result. As mentioned earlier, those with previous cartilage resurfacing techniques had a poorer outcome. However, other factors appeared to play a part. Table XVI shows the difference between these groups in terms of their age, defect size, duration of symptoms leading up to surgery and number of surgical procedures before implantation. The 81 patients with a good/excellent result at 1 year were younger ($p< 0.05$) and had fewer surgical procedures ($p< 0.05$) before implantation compared to those who had a fair/poor result.

However, although 49 patients who had a fair or poor result had a longer duration of symptoms pre-operatively, the difference is not significant ($p=0.19$). Making a

	GOOD/ EXCELLENT	FAIR/ POOR	P VALUE
MEAN AGE (YRS)	30.6 (range 15-54)	34.16 (range 16-49)	$p<0.05$
MEAN DEFECT SIZE (CM^2)	4.82 (range 1-12.25)	4.82 (range 1-12.5)	No difference
MEAN DURATION OF SYMPTOMS (YRS)	7.12 (range 1-23)	8.58 (range 1-25)	$p=0.19$
NUMBER OF PREVIOUS PROCEDURES	1.86 (range 1-5)	2.71 (range 1-6)	$p<0.05$

Table XVI. Comparison between the Good/excellent group and the Fair/poor group at 1 year and p values following ACI-C.

similar comparison between the good/excellent group and the fair/poor group at 2 years revealed a statistically significant difference in terms of the number of surgical procedures before implantation ($p<0.05$). A similar comparison at 3 years again showed a statistically significant difference in terms of the number of surgical procedures before implantation. At 4 years there was a statistically significant difference between these 2 groups in terms of the defect size ($p<0.05$). The mean defect size of the Fair/Poor group was 4.96 cm^2 (range 2.7 to 6 cm^2) and 2.64 cm^2 (range 1.5 to 5.25cm^2) in the good/excellent group, however only 16 patients were reviewed at the 4-year mark.

Femoral Condylar Defects

Seventy-one patients with 52 medial and 19 lateral femoral condylar defects were reviewed at 1 year. The mean age of the patients was 31.15 years (range 15 to 49 years) with a mean defect size of 4.74 cm^2 (range 1 to 12.5cm^2). The mean duration of symptoms leading up to surgery was 8 years (range 1 to 25 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.24 (range 1 to 6). Fifty-eight patients with 32 medial and 13 lateral femoral condylar defects were reviewed at 2 years and 22 patients with 14 medial and 8 lateral femoral condylar defects were reviewed at 3 years. At 4 years, 10 patients with 5 medial and 5 lateral condylar defects were reviewed. Using the modified Cincinnati Rating system, of those patients who had repairs to defects over the medial femoral condyle, 27 out of a total of 52 patients (52%) reported good or excellent results at 1 year, 18 out of 32 (56%) at 2 years, 7 out of 14 (50%) at 3 years and 2 out of 5 (40%) at 4 years (table XVII). However these results were adversely affected by a group of patients who had an ACI following a previous

TIME OF REVIEW	CLINICAL OUTCOME	MEDIAL FEMORAL CONDYLE	LATERAL FEMORAL CONDYLE
1 YEAR	Excellent	11 *(21%)*	8 *(42%)*
	Good	16 *(31%)*	7 *(37%)*
	Fair	14 *(27%)*	3 *(16%)*
	Poor	11 *(21%)*	1 *(5%)*
	Total	***52 (100%)***	***19 (100%)***
2 YEARS	Excellent	8 *(25%)*	6 *(46.2%)*
	Good	10 *(31%)*	3 *(23%)*
	Fair	7 *(22%)*	2 *(15.4%)*
	Poor	7 *(22%)*	2 *(15.4%)*
	Total	***32 (100%)***	***13 (100%)***
3 YEARS	Excellent	4 *(29%)*	2 *(25%)*
	Good	3 *(21%)*	4 *(50%)*
	Fair	5 *(36%)*	1 *(12.5%)*
	Poor	2 *(14%)*	1 *(12.5%)*
	Total	***14 (100%)***	***8 (100%)***
4 YEARS	Excellent	1 *(20%)*	1 *(20%)*
	Good	1 *(20%)*	2 *(40%)*
	Fair	2 *(40%)*	1 *(20%)*
	Poor	1 *(20%)*	1 *(20%)*
	Total	***5 (100%)***	***5 (100%)***

Table XVII. Clinical results at 1,2,3 and 4 years for patients who had an ACI-C for chondral and osteochondral defects over the medial and lateral femoral condyle of the knee by number and *percentage*.

cartilage resurfacing technique such as mosaicplasty or the matrix support prosthesis. The results not including these patients were as follows, 24 out of a total of 39 patients (61.5%) at 1 year reported good/excellent results, 18 out of 26 (69%) at 2 years and 7 out of 12 (58%) at 3 years. Of the patients who had repairs to defects over the lateral femoral condyle 15 out of a total of 19 (79%) reported good or excellent results at 1 year, 9 out of 13 (69.2%) at 2 years, 6 out of 8 (75%) at 3 years and 3 out of 5 (60%) at 4 years.

Patellar defects

Thirty-nine patients with 27 single facet and 12 with multi-facet defects were reviewed at 1 year. The mean age of the patients was 31.28 years (range 15 to 49 years) with a mean defect size of 5.02 cm^2 (range 1.26 to 12 cm^2). The mean duration of symptoms leading up to surgery was 7.74 years (range 1 to 23 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.07 (range 1 to 6). Twenty-four patients with 18 single facet and 6 with multi-facet defects were reviewed at 2 years and 13 patients with 12 single facet and 1 multi-facet defects were reviewed at 3 years. At 4 years, 5 patients with 4 single and 1 multi-facet defects were reviewed.

Using the modified Cincinnati Rating system, of those patients who had repairs to defects over a single facet of the patella, 20 out of a total of 27 patients (74%) reported good or excellent results at 1 year, 11 out of 18 (61%) at 2 years, 7 out of 12 (58%) at 3 years and 2 out of 4 (50%) at 4 years (table XVIII). Of the patients who had repairs to defects over both facets of the patella, 5 out of a total of 12 (41.6%) reported good or excellent results at 1 year, 1 out of 6 (17%) at 2 years, none at 3 years and 1 out of 1 (100%) at 4 years.

TIME OF REVIEW	CLINICAL OUTCOME	SINGLE FACET PATELLAR DEFECT	MULTI-FACET PATELLAR DEFECT
1 YEAR	Excellent	7 *(26%)*	1 *(8.3%)*
	Good	13 *(48%)*	4 *(33.3%)*
	Fair	3 *(11%)*	4 *(33.3%)*
	Poor	4 *(15%)*	3 *(25%)*
	Total	***27 (100%)***	**12 *(100%)***
2 YEARS	Excellent	6 *(33%)*	1 *(17%)*
	Good	5 *(28%)*	
	Fair	5 *(28%)*	5 *(87%)*
	Poor	2 *(11%)*	
	Total	**18 *(100%)***	**6 *(100%)***
3 YEARS	Excellent	4 *(33%)*	
	Good	3 *(25%)*	
	Fair	5 *(42%)*	1 *(100%)*
	Poor		
	Total	**12 *(100%)***	**1 *(100%)***
4 YEARS	Excellent	1 *(25%)*	1 *(100%)*
	Good	1 *(25%)*	
	Fair	2 *(50%)*	
	Poor		
	Total	**4 *(100%)***	**1 *(100%)***

Table XVIII. Clinical results at 1,2,3 and 4 years for patients who had an ACI-C for chondral and osteochondral defects over the patella (single and multi-facet) by number and *percentage*.

Trochlea defects

Seven patients with defects over the trochlea were reviewed at 1 year. The mean age of the patients was 33.3 years (range 18 to 54 years) with a mean defect size of 4.83 cm^2 (range 2 to 10.5 cm^2). The mean duration of symptoms leading up to surgery was 5.14 years (range 1 to 15 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.29 (range 1 to 5). Six patients were reviewed at 2 years and 4 patients were reviewed at 3 years. There were no patients reviewed at 4 years with defects over the trochlea.

Using the modified Cincinnati Rating system, of those patients who were reviewed at 1 year, 7 out of a total of 7 (100%) patients reported good or excellent results at 1 year, 5 out of 6 (87%) at 2 years and 3 out of 4 (75%) at 3 years (table XIX).

TIME OF REVIEW	CLINICAL OUTCOME	DEFECT OVER THE TROCHLEAR
1 YEAR	Excellent	4
	Good	3
	Fair	
	Poor	
	Total	**7**
2 YEARS	Excellent	5
	Good	
	Fair	1
	Poor	
	Total	**6**
3 YEARS	Excellent	1
	Good	2
	Fair	1
	Poor	
	Total	**4**

Table XIX. Clinical results at 1,2 and 3 years for patients who had an ACI-C for chondral and osteochondral defects over the trochlea.

Multiple defects

Thirteen patients with 2 defects repaired at the time of surgery were reviewed at 1 year. The mean age of the patients was 37.69 years (range 14 to 48 years) with a mean defect size of 4.73 cm^2 (range 0.75 to 12.5 cm^2) per defect. The mean duration of symptoms leading up to surgery was 6.92 years (range 1 to 24 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.15 (range 1 to 5). Seven patients were reviewed at 2 years, 2 were reviewed at 3 years and 1 was reviewed at 4 years.

Using the modified Cincinnati Rating system, of those patients who were reviewed at 1 year, 7 out of a total of 13 (54%) patients reported good or excellent results, 4 out of 7(54%) at 2 years, 1 out of 2 (50%) at 3 years and 1 out of 1 (100%) at 4 years (table XX).

TIME OF REVIEW	CLINICAL OUTCOME	MULTIPLE DEFECTS
1 YEAR	Excellent	3
	Good	4
	Fair	3
	Poor	3
	Total	**13**
2 YEARS	Excellent	1
	Good	3
	Fair	2
	Poor	1
	Total	**7**
3 YEARS	Excellent	
	Good	1
	Fair	
	Poor	1
	Total	**2**
4 YEARS	Excellent	1
	Good	
	Fair	
	Poor	
	Total	**1**

Table XX. Clinical results at 1,2,3 and 4 years for patients who had an ACI-C for multiple chondral and osteochondral defects of the knee.

Traumatic Defects

Of the 130 patients reviewed at 1 year, 52 (40%) had defects of traumatic origin. The mean age of the patients was 32.7 years (range 15 to 49 years) with a mean defect size of 4.58 cm^2 (range 1 to 12.5 cm^2). The mean duration of symptoms leading up to surgery was 5.9 years (range 1 to 25 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.23 (range 1 to 6). Thirty-seven patients were reviewed at 2 years, 19 at 3 years and 8 at 4 years. Using the modified Cincinnati Rating system, of those patients who were reviewed at 1 year, 36 out of a total of 52 (69.2%) patients reported good or excellent results, 22 out of 37 (59%) at 2 years, 14 out of 19 (73.7%) at 3 years and 7 out of 8 (87.5%) at 4 years (table XXI) .

TIME OF REVIEW	CLINICAL OUTCOME	TRAUMATIC DEFECTS
1 YEAR	Excellent	15 *(28.8%)*
	Good	21 *(40.4%)*
	Fair	9 *(17.3%)*
	Poor	7 *(13.5%)*
	Total	***52 (100%)***
2 YEARS	Excellent	13 *(35%)*
	Good	9 *(24%)*
	Fair	8 *(22%)*
	Poor	7 *(19%)*
	Total	***37 (100%)***
3 YEARS	Excellent	6 *(31.6%)*
	Good	8 *(42.1%)*
	Fair	3 *(15.8%)*
	Poor	2 *(10.5%)*
	Total	**19 *(100%)***
4 YEARS	Excellent	4 *(50%)*
	Good	3 *(37.5%)*
	Fair	
	Poor	1 *(12.5%)*
	Total	***7 (100%)***

Table XXI. Clinical results at 1,2,3 and 4 years for patients who had defects of traumatic origin, by number and *percentage* following ACI-C.

Osteochondritis dissecans

Of the 130 patients reviewed at 1 year, 18 (13.8%) had defects attributed to osteochondritis dissecans. The mean age of the patients was 26.4 years (range 15 to 44 years) with a mean defect size of 4.42 cm^2 (range 1 to 11.25 cm^2). The mean duration of symptoms leading up to surgery was 8.2 years (range 1 to 23 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 1.5 (range 1 to 3). Eleven patients were reviewed at 2 years, 6 at 3 years and 3 at 4 years. Using the Modified Cincinnati Rating system, of those patients who were reviewed at 1 year, 14 out of a total of 18 (77.7%) patients reported good or excellent results, 9 out of 11 (82%) at 2 years, 3 out of 6 (50%) at 3 years and 1 out of 3 (33%) at 4 years (table XXII).

TIME OF REVIEW	CLINICAL OUTCOME	OSTEOCHONDRITIS DISSECANS
1 YEAR	Excellent	11
	Good	3
	Fair	3
	Poor	1
	Total	**18**
2 YEARS	Excellent	6
	Good	3
	Fair	1
	Poor	1
	Total	**11**
3 YEARS	Excellent	2
	Good	1
	Fair	2
	Poor	1
	Total	**6**
4 YEARS	Excellent	
	Good	1
	Fair	2
	Poor	
	Total	**3**

Table XXII. Clinical results at 1,2,3 and 4 years for patients who had defects attributed to osteochondritis dissecans, following ACI-C.

Chondromalacia Patellae

Of the 130 patients reviewed at 1 year, 23 (17.7%) had defects attributed to chondromalacia patellae. The mean age of the patients was 29.7 years (range 17 to 45 years) with a mean defect size of 4.56 cm^2 (range 1.26 to 10.35 cm^2). The mean duration of symptoms leading up to surgery was 8.9 years (range 1 to 18 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.26 (range 1 to 6). Twelve patients were reviewed at 2 years, 7 at 3 years and 2 at 4 years.

Using the modified Cincinnati Rating system, of those patients who were reviewed at 1 year, 14 out of a total of 23 (61%) patients reported good or excellent results, 4 out of 12 (33%) at 2 years, 3 out of 7 (43%) at 3 years and both patients reviewed at 4 years reported a fair result (table XXIII).

TIME OF REVIEW	CLINICAL OUTCOME	CHONDROMALACIA PATELLAE
1 YEAR	Excellent	2
	Good	12
	Fair	4
	Poor	5
	Total	**23**
2 YEARS	Excellent	1
	Good	3
	Fair	6
	Poor	2
	Total	**12**
3 YEARS	Excellent	1
	Good	2
	Fair	4
	Poor	
	Total	**7**
4 YEARS	Excellent	
	Good	
	Fair	2
	Poor	
	Total	**2**

Table XXIII. Clinical results at 1,2,3 and 4 years for patients who had defects attributed to chondromalacia patellae following ACI-C.

ACI following failed cartilage repair techniques

Of the 130 patients reviewed at 1 year, 17 (13.1%) had an ACI following a failed cartilage resurfacing technique such as mosaicplasty or a matrix support prosthesis of carbon fibre. The mean age of the patients was 35.2 years (range 28 to 48 years) with a mean defect size of 6.64 cm^2 (range 2 to 12.25 cm^2). The mean duration of symptoms leading up to surgery was 12.5 years (range 5 to 25 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 3.29 (range 2 to 6). Nine patients were reviewed at 2 years, 3 at 3 years and none at 4 years. Using the modified Cincinnati Rating system, of those patients who were reviewed at 1 year, 4 out of a total of 17 (24%) patients reported good or excellent results, 1 out of 9 (11%) at 2 years and 1 out of 3 (33%) at 3 years (table XXIV).

TIME OF REVIEW	CLINICAL OUTCOME	ACI FOLLOWING FAILED CARTILAGE REPAIR
1 YEAR	Excellent	1
	Good	3
	Fair	5
	Poor	8
	Total	**17**
2 YEARS	Excellent	1
	Good	
	Fair	5
	Poor	3
	Total	**9**
3 YEARS	Excellent	
	Good	1
	Fair	2
	Poor	
	Total	**3**

Table XXIV. Clinical results at 1,2 and 3 years for patients who had an ACI-C repair following a failed cartilage resurfacing technique.

Arthroscopic review

A repeat arthroscopy at 1 year following the implantation revealed ICRS grades of 1 or 2 in 84 of 100 patients (84%). The arthroscopy of 4 patients did not show any evidence of the graft and scored an ICRS of 4 (table XXV). Thirty-two arthroscopies were carried out at the 2-year review, which revealed ICRS grades of 1 or 2 in 27 of 32 patients (84%). In the case of 1 patient there was no evidence of the graft and scored 4 on the ICRS grading system. Further review arthroscopies were not carried out unless there was a clinical indication. Of the 34 biopsies taken at the time of the 1-year check arthroscopy, 21 were from the medial femoral condyle, 7 from the lateral femoral condyle, 4 from the patella and 2 from the trochlea. Of the 13 biopsies taken at the time of the 2-year check arthroscopy, 5 were taken from the medial femoral condyle, 3 from the lateral femoral condyle, 4 from the patella and 1 from the trochlea.

Hyaline cartilage of normal appearance was found in 7 of the biopsies taken at 1 year, consisting of cells in lacunae enveloped within a matrix that stained positively for type II collagen using Safranin O. Of the remaining biopsies taken at 1 year, 10 showed characteristics of both hyaline and fibrocartilage and 17 showed evidence of fibrocartilage (table XXVI).

Of those repairs biopsied at 2 years, 3 showed evidence of hyaline cartilage, 5 mixed hyaline and fibrocartilage and 5 fibrocartilage.

One of the grafts which showed mixed hyaline and fibrocartilage at 1 year, when biopsied again at 2 years revealed hyaline cartilage alone. This suggests that grafts can take up to 2 years to fully mature as suggested previously by Bentley [89] and Peterson [91].

ICRS GRADE	NUMBER (%)	
	1 YEAR	2 YEARS
1, Excellent	12 *(12%)*	1 *(3%)*
2, Good	72 *(72%)*	26 *(81%)*
3, Fair	12 *(12%)*	4*(13%)*
4, Poor	4 *(4%)*	1 *(3%)*
Total	100 *(100%)*	32 *(100%)*

Table XXV. Arthroscopic results at 1 and 2 years, by number and *percentage* following ACI-C.

	BIOPSY RESULT AT 1 YEAR	
CLINICAL RESULT	HYALINE OR MIXED HYALINE AND FIBROCARTILAGE	FIBROCARTILAGE
Excellent	6	6
Good	7	6
Fair	4	2
Poor		3

Table XXVI. Clinical results of patients based on their biopsy result at 1 year, following ACI-C.

Patients biopsied at 1 year who had a hyaline or mixed repair had a better clinical result than those biopsied at 1 year who had a fibrocartilage repair. Of the 17 patients who had a hyaline or mixed repair, 76.5% reported good or excellent results at 1 year compared with the 17 patients that had a fibrocartilage repair who reported 70.5% good or excellent results. However, this difference did not reach statistical significance (p=0.40). At 1 year of the 34 patients who were biopsied, 3 patients had a poor clinical result based on the modified Cincinnati rating system, all of whom had a fibrocartilage repair when biopsied (table XXVI).

COMPLICATION	NUMBER
MAJOR	
Deep vein thrombosis	2 at 1 year
Graft failure	1 at 1 year 2 at 2 years 1 at 3 years
INTERMEDIATE	
Graft hypertrophy	11 at 1 year 4 at 2 years 2 at 4 years
MINOR	
Stitch abscess	1 at 1 year
Slow to mobilize requiring a manipulation under anaesthetic	11 at 1 year
Unplanned arthroscopy	9 at 1 year 2 at 4 years

Table XXVII. Complications following the ACI-C.

Complications

Within the first year following chondrocyte implantation there were 3 (2.3%) major complications and 32 (24.6%) intermediate and minor complications. Within the 2nd year of transplantation there were 2 (2.4%) major complications and 4 (4.9%) intermediate and minor complications. Within the 3rd year there was 1 (2.4%) major complication and no intermediate or minor complications and within the 4th year there were no major complications and 4 intermediate and minor complications (table XXVII).

Complications encountered within the 1st year included, two patients who developed a deep vein thrombosis and required anticoagulation with warfarin and one patient whose graft failed at the 1 year mark. Eleven patients were slow to mobilize and required a manipulation under anaesthetic. Eleven patients had hypertrophy of the graft at the time of the check arthroscopy at 1 year. Nine patients had an unplanned arthroscopy within the first year, 1 for graft hypertrophy, 2 who required division of adhesions, 1 for a torn meniscus, 2 for ongoing pain, 1 for excision of a plica and 2 patients required an arthroscopy since an infective process was suspected but nothing was grown in culture. One patient had a stitch abscess that resolved with a course of oral antibiotics.

At 2 years, there were 2 episodes of graft failure and 4 patients required shaving of their grafts, which had hypertrophied.

At 3 years there was 1 patient who required an arthroscopy for ongoing pain and it was found that the graft had failed.

At 4 years there were 2 patients who required an arthroscopy for shaving of hypertrophied grafts.

Discussion

Autologous chondrocyte implantation using a type I/III collagen membrane offers an alternative to a periosteum cover in containing cultured chondrocytes within a chondral or osteochondral defect. Peterson et al [91] has suggested that the periosteum not only provides a membrane preventing the leakage of implanted cells but also contributes growth factors and cells to the graft repair. This view has been supported by observations made using an animal model [157] but has not been demonstrated in the human subject as previously discussed. An alternative to a periosteal covering was sought due to concerns of the possible co-morbidity associated with harvesting the periosteum and also problems with its hypertrophy requiring an arthroscopy and shaving (see Chapter 3, pages 127-129).

The results of this study are encouraging with 68% of patients reporting good or excellent results at 1 year, 64% at 2 years, 61% at 3 years and 56% at 4 years (not including the group who previously had cartilage resurfacing techniques such as mosaicplasty or a matrix support prosthesis). Although this would suggest a clinical deterioration following transplantation the decrease in good or excellent scores over the 4 year period was not statistically significant. ($p=0.70$).

The findings at the 1 and 2 year check arthroscopies revealed that 84% of those who were arthroscoped had repairs that were good or excellent based on the ICRS grading system. At 1 year 4 grafts had failed, 2 occurred with defects over the retropatellar surface, 1 over the lateral femoral condyle and 1 over the medial femoral condyle. At 2 years 1 graft failed which was located over the retropatellar surface. Although the majority of graft failures occurred in patients with defects located over the retropatellar surface this was not typical of the group as a whole,

with 64% of patients at 1 year reporting good or excellent results. However, patients with repairs to single facet defects (74%) did better than those with repairs to both facets (41.6%).

As for the periosteal covered ACI, it became apparent that there were a number of factors that influenced the outcome of the repair. A comparison between the good/excellent group and fair/poor group at 1,2 and 3 years revealed that patients who had fewer surgical procedures leading up to the implantation did better and those that had previous cartilage resurfacing techniques such as mosaicplasty did worse. Other factors that seemed to affect the outcome of the implantation included the age of the patient, with patients older than 34 years having a worse outcome and the size of the defect that was repaired. At 1-year, patients who were younger and at 4 years those that had smaller defects did better.

Defects repaired in this study were larger than those repaired in other studies. The mean defect size of the femoral condyle lesions in Peterson et al's [72] recent long-term durability study was 3.4cm² compared with 4.74cm² in this study. Similarly, simple defects that were repaired in Minas' study [167] had a mean size of 4.3 cm². The difference in the size of the defects repaired over the medial femoral condyle may explain why our results (69% good or excellent at 2 years) are not as good as the Swedish experience [72] (89% good or excellent at 2 years). Although Peterson et al use 5 scoring systems in their study to evaluate the patients' clinical outcome, it is not clear which system they use to arrive at this figure, so it is difficult to make a direct comparison.

Patients referred for chondrocyte implantation to the Swedish group had a shorter duration of symptoms (3.4 years) [72] compared to our patients (8 years). This may account for the defects in our group being bigger since patients have had them for

longer. The majority of our patients are referred via other institutions and regrettably results in a delay in them receiving surgical intervention. Possibly this delay results in the defect getting bigger and may have a deleterious psychological effect although this has not been quantified.

Patients' age, size of the defect, number of operations before implantation and duration of symptoms leading up to surgery may all play a role in the clinical outcome following chondrocyte implantation and may have implications for patient selection for this technique. This requires further analysis.

Concerns have been raised about the insertion of multiple sutures into the surrounding cartilage at the margin of the defect resulting in damage to the articular surface. Similar to the periosteal covered ACI there was no evidence in this study to suggest that this was the case. At the check arthroscopies at 1 and 2 years the articular cartilage adjacent to the graft was intact and appeared healthy. Of more concern with this technique was the length of time it took to attach the membrane to the rim of the defect resulting in relatively long tourniquet and anaesthetic times of up to 2 hours.

Repairs to areas of the knee that have been considered difficult in the past have also had good results. Defects over the lateral femoral condyle can be difficult to access using this technique. However, at 1 year 79% of patients reported good or excellent results and 75% at 3 years. Although the patients with defects over the lateral femoral condyle were a small group the results are encouraging. Similarly, patients who had repairs to the trochlea did well with 100% of patients reporting good or excellent results at 1 year, 87% at 2 years and 75% at 3 years, although these are encouraging results the group was small with only 7 patients reviewed at 1 year.

Patients with traumatic defects and those with osteochondritis dissecans did better than those with chondromalacia patellae or had defects repaired previously by other resurfacing techniques. The results for the last group were disappointing with 24% reporting good or excellent results at 1 year, 11% at 2 years and 33% at 3 years. The defects repaired in this group were considerably bigger (mean 6.64 cm^2) and were often quite deep. These patients also had a longer duration of symptoms compared with other groups (12.5 years) and had multiply operated knees (3.29 operations before implantation). As previously mentioned, all these factors probably play an important role in the final outcome of chondrocyte implantation.

A review of the histology at 1 and 2 years following the chondrocyte implantation revealed that this technique can result in a hyaline repair with 7 out of 34 biopsies showing hyaline cartilage alone and 10 showed a mixture of hyaline and fibrocartilage. At 2 years, 3 biopsies showed evidence of hyaline cartilage alone and 5 showed mixed hyaline and fibrocartilage. These encouraging results support the findings published by Briggs et al [90] for this technique. In this review patients that had a hyaline or mixed repair, reported a better clinical result than those that had a fibrocartilage repair at 1 year, although this did not achieve statistical significance.

There is considerable speculation about the maturing process which might occur in the graft, so that a graft that appears fibrous or fibrocartilaginous or a mixture of hyaline and fibrocartilage at 1 year, may mature to hyaline cartilage at 2 years [89;91]. In this study there was a case of 1 patient when biopsied at 1 year having a mixture of hyaline and fibrocartilage but at 2 years the same patient had hyaline cartilage alone. Although both biopsies were taken from the graft, there maybe

considerable variability in the histological appearance of the graft from one area to the next, which may account for this apparent change. Further long-term studies are required to clarify this point.

In summary, our study has shown that the ACI technique using a type I/III biodegradable porcine membrane rather than a periosteal cover can result in a hyaline repair of chondral and osteochondral defects. There was a significant improvement in the Modified Cincinnati scores at each of the clinical reviews from years 1 to 4 especially for the post-traumatic, trochlea and patella defects, with 84% having good or excellent repairs as judged on the ICRS grading system at the follow up arthroscopies.

However, not all patients may be suitable for this technique and factors such as the patients' age, defect size, duration of symptoms leading up to surgery and number of surgical procedures before implantation appear to be important in patient selection.

CHAPTER 5:

A PROSPECTIVE, RANDOMISED STUDY COMPARING TWO TECHNIQUES OF AUTOLOGOUS CHONDROCYTE IMPLANTATION FOR OSTEOCHONDRAL DEFECTS IN THE KNEE: Periosteum covered versus type I/III collagen covered

Introduction

The previous 2 chapters have described 2 techniques to retain the cultured chondrocyte suspension within an osteochondral defect. As already mentioned Brittberg et al [36] used a periosteal cover sutured to the rim of the defect (ACI-periosteum) whereas other authors have used a type I/III collagen cover which was similarly attached to the rim of the defect (ACI-collagen) [89;90]. There is considerable speculation as to whether the periosteal cover acts simply as a watertight seal or whether it secretes factors essential for the development of a hyaline cartilage repair [122]. The results have been encouraging for both techniques (see previous chapters), but there are no prospective, randomised controlled trials, which compare the two techniques. This study compares ACI-periosteum and ACI-collagen for the repair of chondral and osteochondral defects over the femoral condyles, patella and trochlea at 2 years. This comparison was made at 2 years since both Bentley et al [89] and Peterson et al [91] have suggested that grafts can take this long to mature to a hyaline-like repair.

Patients and Methods

The South East Multi-Centre Research Ethics Committee and The Joint Research and Ethical Committee of the Royal National Orthopaedic Hospital Trust gave its

approval before commencing this study (G. Bentley 2002 – personal communication).

Between March 1999 and February 2002, a total of 68 patients with a mean age of 30.52 years (range 15 to 52 years) with symptomatic articular cartilage defects were randomised to have either ACI with a periosteum cover (33 patients) or ACI with a type I/III synthetic cover (35 patients). There were 33 men and 35 women with a mean age of 30.52 years (range 15 to 52 years) for those that underwent the ACI with periosteum technique and 30.54 years (range 16 to 49 years) for those that underwent the ACI technique with a type I/III collagen cover. The mean defect size was 4.54 cm^2 (range 1 to 12 cm^2) with 38 having defects in the right knee and 30 in the left. Of the 68 patients, 26 (38%) defects were on the medial femoral condyle, 27 (40%) on the patella, 11 (16%) on the lateral femoral condyle, and 4 (6%) on the trochlea (table XXVIII). The aetiology of the lesions included 34 (43%) patients who had post traumatic defects, 20 (29%) patients had chondromalacia patellae, 12 (18%) had osteochondritis dissecans and 7 (10%) had defects of unknown aetiology, although they were most probably post traumatic (table XXIX).

The mean duration of symptoms was 7.09 years (range 1 to 27 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.09 (range 1 to 8). All patients were followed up at 24 months.

The indication for surgery in all cases was disabling pain associated with a chondral or osteochondral defect. Other symptoms included swelling, giving way, catching and locking.

ANATOMICAL DISTRIBUTION	TOTAL	PERIOSTEUM COVERED ACI	COLLAGEN COVERED ACI
Medial femoral condyle	26 *(38%)*	8 *(24%)*	18 *(51%)*
Patella	27 *(40%)*	20 *(61%)*	7 *(20%)*
Lateral femoral condyle	11 *(16%)*	3 *(9%)*	8 *(23%)*
Trochlea	4 *(6%)*	2 *(6%)*	2 *(6%)*
Total	**68 *(100%)***	**33 (100%)**	**35 *(100%)***

Table XXVIII. Anatomical site of the defects found in 68 patients, by number and *percentage* for the ACI-C vs ACI-P study.

AETIOLOGY OF DEFECTS	TOTAL	PERIOSTEUM COVERED ACI	COLLAGEN COVERED ACI
Trauma	29 *(43%)*	12 *(36%)*	17 *(49%)*
Osteochondritis dissecans	12 *(18%)*	5 *(15%)*	7 *(20%)*
Chondromalacia patellae	20 *(29%)*	15 *(46%)*	6 *(17%)*
Other	7 *(10%)*	1 *(3%)*	5 *(14%)*
Total	**68 *(100%)***	**33 *(100%)***	**35 *(100%)***

Table XXIX. Aetiology of the defects found in 68 patients, by number and *percentage* for the ACI-C vs ACI-P study.

Surgical Technique

The surgical technique for the periosteal covered ACI and the collagen covered technique (figure XXI) have already been described on pages 106-108 and pages 140-141 respectively.

Patients were randomised using random sample numbers in sealed envelopes.

Rehabilitation

The rehabilitation programme was identical for both techniques and has been previously described on page 108-109.

Evaluation

Patients were evaluated clinically and arthroscopically as described on pages 109-111.

Statistical analysis. The sample size and power calculation were based on 30 patients in each group with an expected 2 year Cincinnati score of 43 to 91 in the collagen covered ACI group and between 38 and 86 in the periosteum covered ACI group. Thus, an expected difference of 20 between the 2 groups was considered clinically significant and a power of 90% was assumed.

Statistical comparison of the pre-operative and postoperative clinical assessment scores at 2 years for each of the techniques was by the paired Students T test. Comparison of outcome scores between the groups was made using the unpaired Student T test. A p value of less than 0.05 was considered statistically significant.

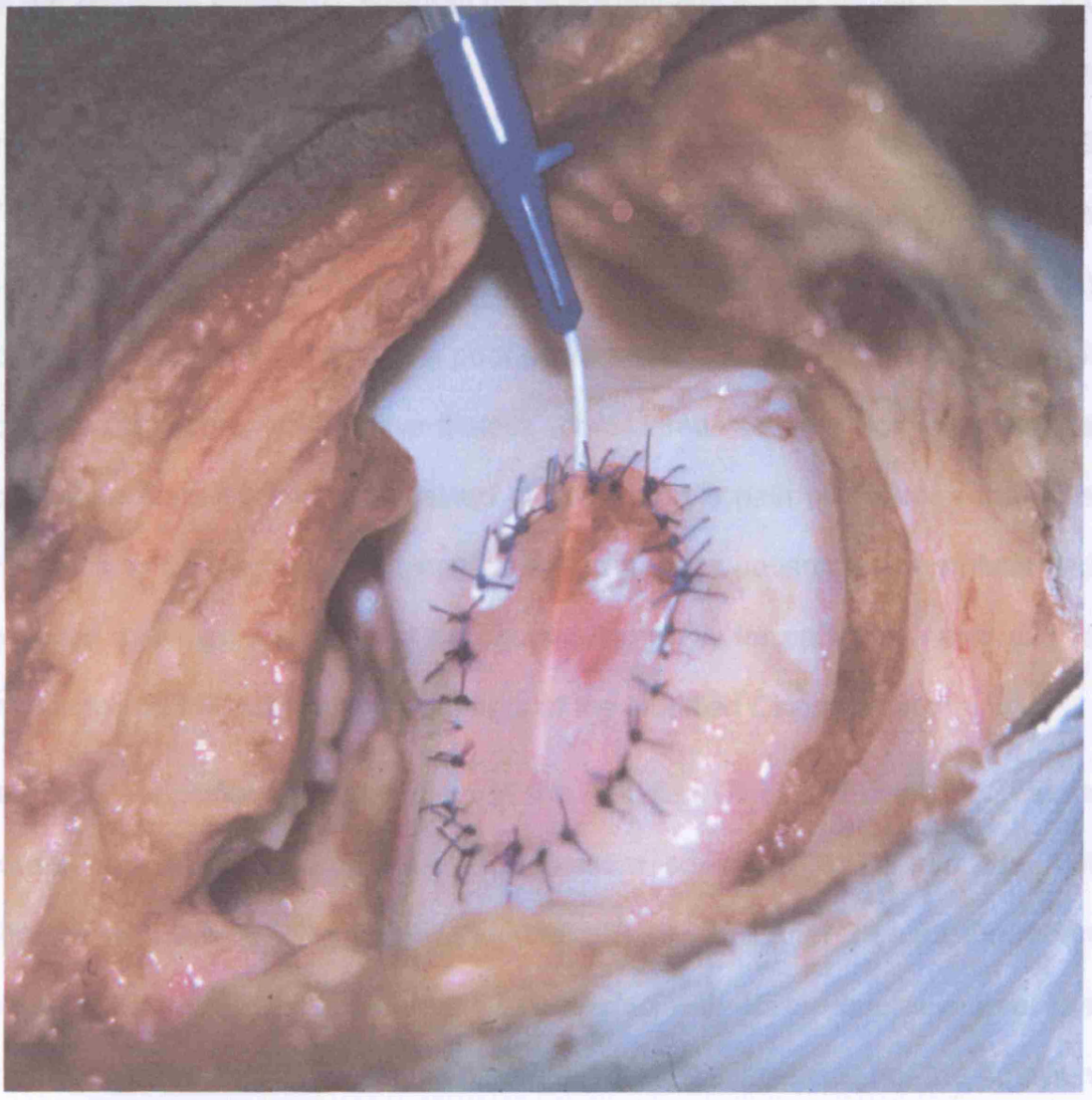

Figure XXI. Photograph of a type I/III collagen membrane secured to the rim of an osteochondral defect located over the medial femoral condyle. A cannula has been introduced through a small opening underneath the membrane so that a suspension of cultured chondrocytes can be injected into the defect.

(Courtesy of G. Bentley)

Results

Clinical Review

The pre-operative modified Cincinnati rating system scores are shown in table XXX for both techniques. Out of a total of 33 patients who had the ACI technique with periosteum cover, 13 (39.4%) had a good score, 11 (33.3%) had a fair score and 9 (27.3%) had a poor score pre-operatively. Out of a total of 35 patients who had the ACI technique with a type I/III collagen cover 12 (34%) had a good score, 15 (43%) had a fair score and 8 (23%) had a poor score pre-operatively. Those patients that had a good score were nevertheless considered suitable for chondrocyte implantation because they complained of considerable pain on exertion that was attributable to their articular cartilage defects. All these patients were athletic and functioned at a high level so that despite scoring badly for pain they were able to compensate on the remaining parameters of the Modified Cincinnati score.

There was a significant improvement in the modified Cincinnati score at 2 years following the ACI technique with a periosteum cover ($p<0.005$) and the ACI technique with a type I/III collagen membrane ($p<0.005$). After 2 years the mean modified Cincinnati knee score was 62 compared with 45 pre-operatively for the periosteum covered ACI group, this represented a 38% increase. For the collagen covered ACI group the mean modified Cincinnati score was 67 at 2 years compared with 45 pre-operatively, this represented a 49% increase. Hence the difference of the means at 2 years for the 2 groups was 5 with a 95% confidence interval that the true mean Cincinnati score for the ACI-collagen group at 2 years lies between 55 and 79. There was no statistically significant difference between the 2 groups (p value = 0.367).

	TOTAL	EXCELLENT	GOOD	FAIR	POOR
ACI (PERIOSTEAL COVER)	33		13 *(39.4%)*	11 *(33.3%)*	9 *(27.3%)*

	TOTAL	EXCELLENT	GOOD	FAIR	POOR
ACI (COLLAGEN COVER)	35		12 *(34%)*	17 *(43%)*	11 *(23%)*

Table XXX. Modified Cincinnati scores before surgery, for the ACI-C vs ACI-P study.

	TOTAL	EXCELLENT	GOOD	FAIR	POOR
ACI (PERIOSTEAL COVER)	33	10 *(30.3%)*	12 *(36.4%)*	7 *(21.2%)*	4 *(12.1%)*

	TOTAL	EXCELLENT	GOOD	FAIR	POOR
ACI (COLLAGEN COVER)	35	12 *(34.3%)*	14 *(40%)*	5 *(14.3%)*	4 *(11.4%)*

Table XXXI. Modified Cincinnati scores at 2 years following the ACI technique with either a periosteum covering or type I/III collagen covering.

Based on the Cincinnati score, of the 35 patients with defects treated by the collagen covered ACI technique, 26 (74%) had a good or excellent result (table XXXI) compared with 22 of 33 (67%) patients treated by ACI with a periosteum cover.

Table XXXII shows the results at 2 years based on the site of the defect. Of the 18 defects of the medial femoral condyle treated by ACI-collagen, 13 (72%) had a good or excellent result compared with 5 (62.5%) out of 8 treated by ACI-periosteum ($p>0.05$). However, this difference was not significant. In the case of defects of the lateral femoral condyle, 6 (75%) out of 8 had a good or excellent result following the ACI-collagen technique compared with 3 out of 3 after ACI-periosteum ($p>0.05$). For defects over the patellar 6 out of 7 (86%) had a good or excellent result following ACI-collagen compared with 12 out of 20 (60%) following ACI-periosteum ($p>0.05$). The numbers of defects of the trochlea were too small for statistical analysis.

All patients were randomized as previously described, however it is clear from the data analysis that more patients who underwent the periosteum covered ACI had defects over the patella, a group which are notorious for being difficult to treat ([1,2]). This anomaly occurred purely by chance and could represent a confounding factor of the study. This point will be referred to again in the discussion.

ANATOMICAL DISTRIBUTION	TOTAL	EXCELLENT	GOOD	FAIR	POOR	P VALUE
MFC						
ACI (periosteum)	8	1	4	2	1	
ACI (collagen membrane)	18	5	8	2	3	p>0.05
LFC						
ACI (periosteum)	3	2	1			
ACI (collagen membrane)	8	4	2	1	1	p>0.05
Patella						
ACI (periosteum)	20	6	6	5	3	
ACI (collagen membrane)	7	2	4	1		p>0.05
Trochlea						
ACI (periosteum)	2	1	1			
ACI (collagen membrane)	2	1		1		

Table XXXII. Clinical results at 2 years for 68 patients who had either an ACI with a periosteum cover or an ACI with a collagen membrane cover for osteochondral defects of the knee. (MFC = Medial femoral condyle and LFC = Lateral femoral condyle).

Arthroscopic Review

A repeat arthroscopy was made at the 1 and 2 year mark following the chondrocyte implantation. Of the 35 patients who had an ACI-collagen technique 29 had a repeat arthroscopy at 1 year (table XXXIII), 23 (79%) had an ICRS grade of 1 or 2 compared with 25 (81%) patients out of 31 who had the ACI-periosteum technique. At 2 years 11 patients who had the ACI-collagen technique had a repeat arthroscopy of whom 9 (82%) had an ICRS grade of 1 or 2. After the ACI-periosteum technique 9 patients had a repeat arthroscopy at 2 years, which revealed that 5 (55.6%) had an ICRS grade of 1 or 2. This difference was not significant ($p>0.05$). At 1 year the majority of grafts following either the ACI-collagen technique or the ACI-periosteum technique completely filled the defects with evidence of good incorporation into the surrounding articular surface resulting in a high ICRS score. However, at 1 year the grafts were relatively soft on probing compared with the surrounding cartilage but at 2 years the grafts did appear firmer.

Of the 13 biopsies taken from the ACI-collagen patients at the time of the 1 year check arthroscopy, 8 were from the medial femoral condyle, 3 were from the lateral femoral condyle, 1 was from the patella and 1 from the trochlea. Hyaline cartilage was found in 3 of the biopsies taken at this time (figure XXIII), consisting of chondrocytes in lacunae enveloped within a matrix that stained positively for Safranin O (figure XXII, XXIV). Of the remaining biopsies taken at 1 year, 6 showed both hyaline cartilage and fibrocartilage and 4 showed fibrocartilage alone. At 2 years 7 biopsies were taken from grafts following the ACI-collagen technique, 1 showed hyaline cartilage, 4 showed a mixture of hyaline and fibrocartilage and 2 showed fibrocartilage. At 1 year following the ACI-periosteum technique 14 biopsies were taken at the time of the repeat arthroscopy, 5 were taken from the

medial femoral condyle, 8 from the patella, and 1 from the lateral femoral condyle. Two showed hyaline cartilage, 4 showed a mixture of hyaline and fibrocartilage, and 8 showed fibrocartilage. At 2 years 3 biopsies were taken following the ACI-periosteum technique 1 showed hyaline cartilage and 2 showed a mixture of hyaline and fibrocartilage (table XXXIV).

One of the grafts following the ACI-periosteum technique showed mixed hyaline and fibrocartilage at 1 year, when biopsied again at 2 years revealed hyaline cartilage alone. This observation would support previous suggestions [89;91] that grafts may take up to 2 years to fully mature.

ICRS GRADE	ACI-COLLAGEN		ACI- PERIOSTEUM	
	1 YEAR	2 YEARS	1 YEAR	2 YEARS
1, Excellent	3 *(10.3%)*	1 *(9%)*	3 *(9.7%)*	
2, Good	20 *(69%)*	8 *(73%)*	22 *(71%)*	5 *(55.5%)*
3, Fair	5 *(17.2%)*	2 *(18%)*	5 *(16%)*	3 *(33.3%)*
4, Poor	1 *(3.4%)*		1 *(3.2%)*	1 *(11.1%)*
Total	29 *(100%)*	11 *(100%)*	31 *(100%)*	9 *(100%)*

Table XXXIII. Arthroscopic results at 1 and 2 years for patients who had either and ACI with a periosteum cover or ACI with a type I/III collagen cover, by number and *percentage*.

BIOPSY RESULT	ACI-COLLAGEN		ACI- PERIOSTEUM	
	1 YEAR	2 YEARS	1 YEAR	2 YEARS
Hyaline	3 *(23%)*	1 *(14%)*	2 *(14.2%)*	1 *(33.3%)*
Mixed hyaline and fibrocartilage	6 *(46%)*	4 *(57%)*	4 *(28.6%)*	2 *(66.6%)*
Fibrocartilage	4 *(31%)*	2 *(29%)*	8 *(57.1%)*	
Total	13 *(100%)*	7 *(100%)*	14 *(100%)*	3 *(100%)*

Table XXXIV. Biopsy results at 1 and 2 years for patients who had either and ACI with a periosteum cover or ACI with a type I/III collagen cover, by number and *percentage*.

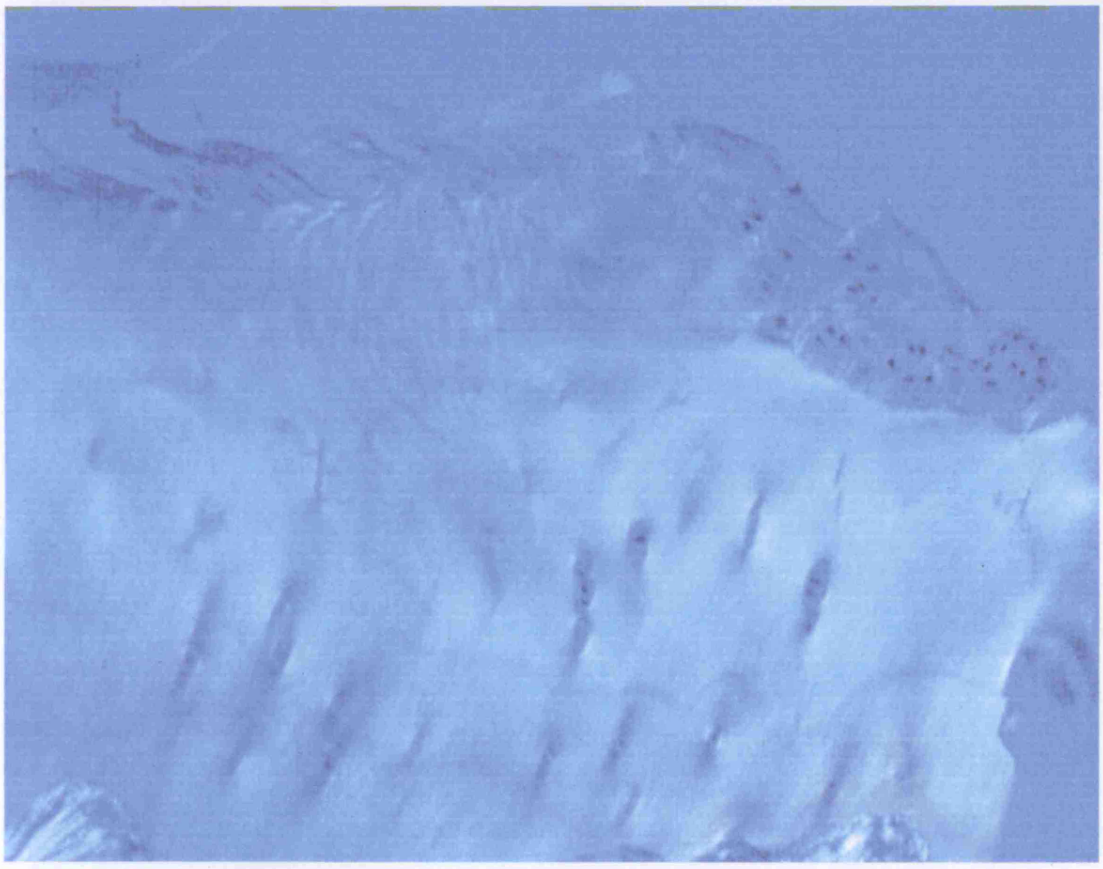

Figure XXII. Photomicrograph taken at the surface of a full thickness core biopsy of repair tissue following an ACI-C procedure at 2 years showing a normal hyaline appearance with orderly columns of chondrocytes (Polarized light ,Safranin O x 34). Patient number 129 (see Appendix III: Table of Results).

Figure XXIII . Photomicrograph of a full thickness core biopsy of repair tissue following an ACI-C procedure at 1 year (Haemophyllin and Eosin stain x 10). Surface of biopsy to the left of the photomicrograph and subchondral bone to the right. Patient number 74 (see Appendix III: Table of Results).

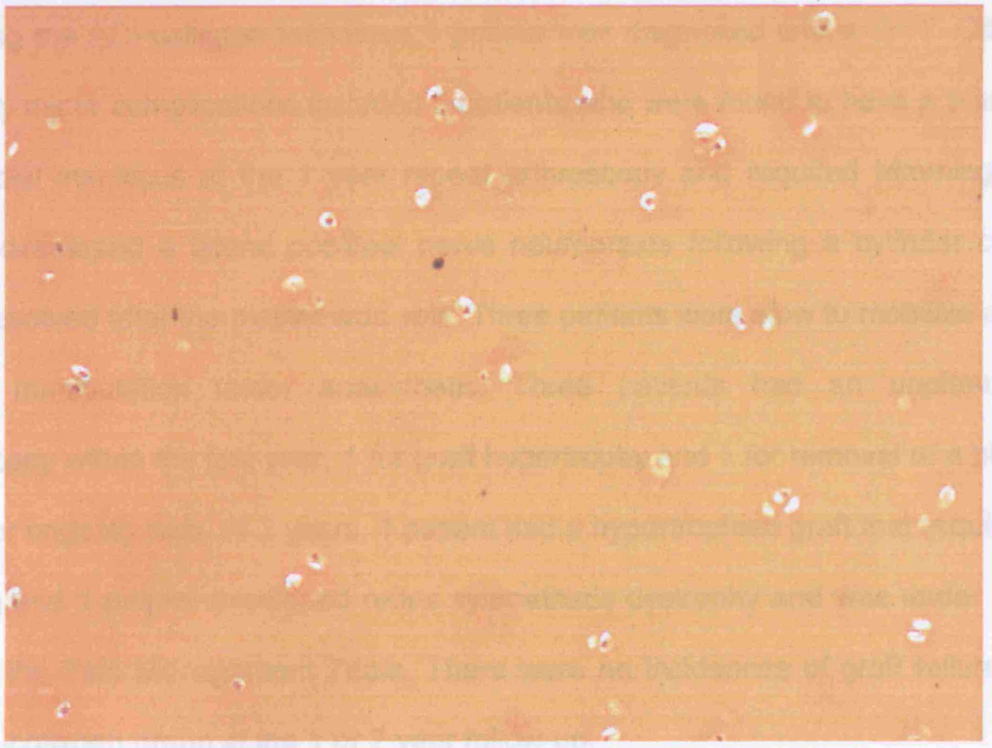

Figure XXIV. Photomicrograph taken of the middle third of a full thickness core biopsy of repair tissue following an ACI-C procedure at 2 years showing chondrocytes in lacunae embedded in a matrix which stains strongly for matrix proteoglycan (Safranin O x 34). Patient number 80 (see Appendix III: Table of Results).

Complications

Within the first year following chondrocyte implantation there were 3 (4%) major complications and 43 (63%) intermediate and minor complications (table XXXV). Following the ACI-collagen technique 1 patient was diagnosed with a DVT. Other relatively minor complications included 3 patients who were found to have a tear of the medial meniscus at the 1 year repeat arthroscopy and required trimming, 1 patient developed a lateral popliteal nerve neuropraxia following a cylinder cast which resolved after the plaster was split. Three patients were slow to mobilize and had a manipulation under anaesthetic. Three patients had an unplanned arthroscopy within the first year, 1 for graft hypertrophy and 1 for removal of a plica and 1 for ongoing pain. At 2 years, 1 patient had a hypertrophied graft that required shaving and 1 patient developed reflex sympathetic dystrophy and was under the care of the Pain Management Team. There were no incidences of graft failure in the ACI-collagen group at the 1 or 2 year follow-up.

Following the ACI-periosteum technique 2 grafts failed within the first year. Other relatively minor complications included 12 patients (36.4%) whose grafts had hypertrophied at the 1 year check arthroscopy (figure XXV), 4 patients (12.1%) who required a manipulation under an anaesthetic since they were unable to flex their operated knee to 90°, 1 patient who developed a superficial wound infection in the immediate post-operative period that responded to oral antibiotics and 1 patient who had a large plica removed at the time of the 1 year arthroscopy. Eight patients (24.2%) required an unplanned arthroscopy within the first year following the ACI-periosteum technique, 4 for graft hypertrophy that required shaving, 2 for ongoing pain, 1 for division of adhesions and 1 for a suspected septic arthritis

however this was ruled out following negative cultures. At 2 years, there was 1 case of graft hypertrophy at the repeat arthroscopy, 1 patient developed reflex sympathetic dystrophy and 3 patients who required an unplanned arthroscopy during the second year, 1 for graft hypertrophy that required shaving and 2 for division of adhesions.

COMPLICATION	NUMBER	
	ACI-COLLAGEN	ACI-PERIOSTEUM
MAJOR	***1 (3%) at 1 year 0 at 2 years***	***2 (6 %) at 1 year 0 at 2 years***
Deep vein thrombosis	1 at 1 year	
Graft failure		2 at 1 year
INTERMEDIATE AND MINOR	***10 (29%) at 1 year 2 (6%) at 2 years***	***26 (79%) at 1 year 5 (15%) at 2 years***
Graft hypertrophy at 1 or 2 year check arthroscopy ***(intermediate complicaton)***	1 at 2 years	12 at 1 year 1 at 2 years
Superficial wound infection		1 at 1 year
Medial meniscal tear requiring shaving	3 at 1 year	
Large plica removed at repeat arthroscopy		1 at year
Lateral popliteal nerve neuropraxia following cylinder cast – resolved	1 at 1 year	
Reflex sympathetic dystrophy	1 at 2 years	1 at 2 years
Slow to mobilise requiring a manipulation under anaesthetic	3 within 1 year	4 within 1 year
Unplanned arthroscopy - graft hypertrophy - division of adhesions - removal of plica - ongoing pain - division of adhesions and graft hypertrophy -? septic arthritis (nil grown)	1 within 1 year 1 within 1 year 1 within 1 year	 4 within 1 year 1 within 2 years 2 within 2 years 2 within 1 year 1 within 1 year 1 within 1 year

Table XXXV. Complications within the first 2 years following autologous chondrocyte implantation with either a periosteum or type I/III collagen cover.

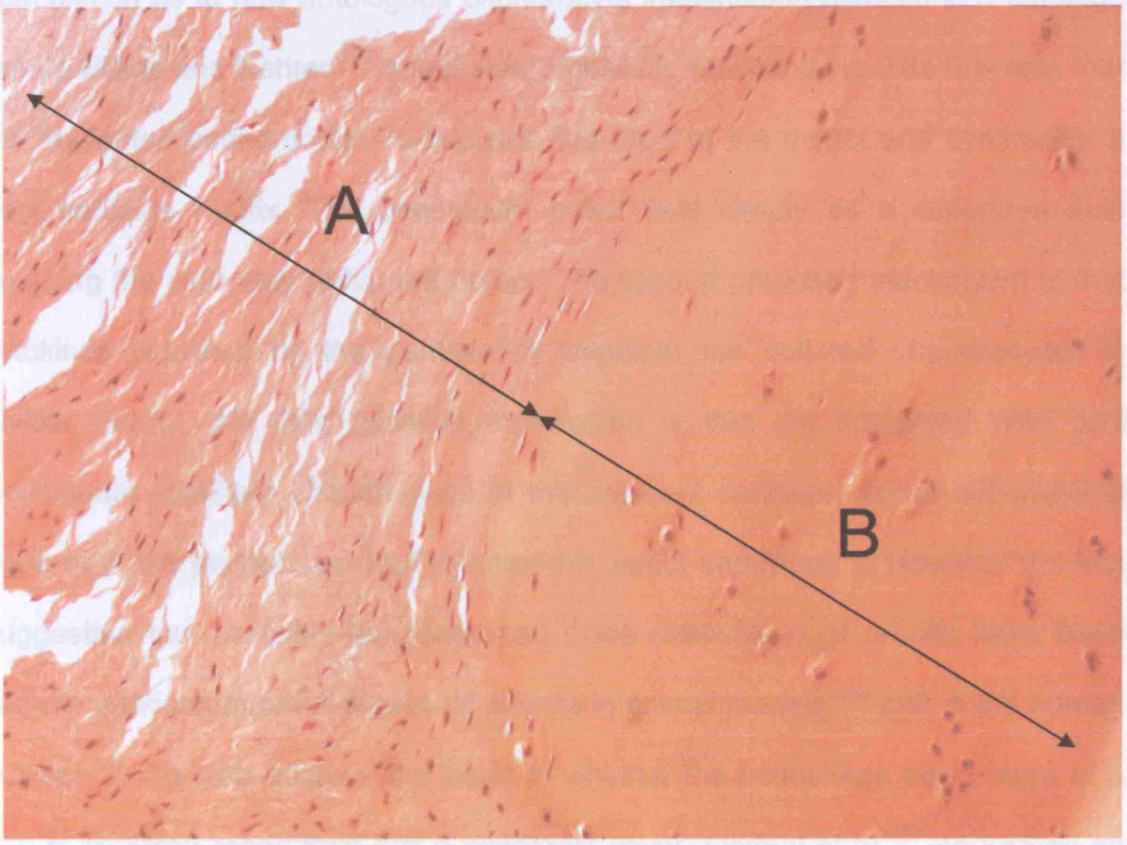

Figure XXV. Photomicrograph taken at the surface of a full thickness core biopsy of repair tissue following an ACI-P procedure at 1 year. This slide shows histological detail at the surface of the repair tissue showing chondrocytes in lacunae embedded within a matrix which stains strongly for matrix proteoglycan, labeled B. At the surface of the graft is seen the remnant of the periosteum cover labeled A (Safranin O x 10). Patient number 15 (see Appendix III: Table of Results).

Discussion

When the ACI technique was first described in the treatment of chondral and osteochondral defects in patients' knees by Brittberg et al [36] a periosteum cover was used to contain the chondrocytes within the defect. This led to some speculation as to how autologous chondrocyte implantation resulted in a cartilage repair. Minas and Nehrer [122] suggested 3 possible mechanisms. The first was that the implanted chondrocytes re-populate the area of the defect and synthesize a new cartilage matrix. The periosteum patch acts simply as a watertight seal ensuring the cells stay within the defect. The second proposed mechanism is that cytokines secreted by the periosteum stimulate the cultured chondrocytes to divide. Finally, the third possible explanation is that the implanted cells and periosteum stimulate chondrocytes in the adjacent cartilage, in the subchondral bone or in the periosteum itself to enter the defect and repair it. However the last suggestion can probably be discounted since relatively poor results have been seen in periosteum patch repairs of defects in animal models [156] and in the human subject [127]. To help address the issue of whether the periosteum plays more of a role in cartilage repair than just a watertight cover, Lindahl et al [157] performed an animal study using rabbits with artificially-created knee osteochondral defects. Dead periosteum (periosteum which had been snap frozen in liquid nitrogen) was sutured to the rim of the defect and a chondrocyte suspension was injected into the defect underneath the periosteum. Only 1 out of 8 rabbits developed good repair tissue. Lindahl concluded that the periosteum and chondrocytes work together to repair the defect. It has also been suggested that in using both periosteum and chondrocytes there appeared to be a chondroprotective effect on the surrounding cartilage since the number of apoptotic cells was reduced by 60% compared with

an untreated defect [158]. However this has not been seen in human subjects but the results seen in rabbits has led to the Swedish Bone and Cartilage Research Group to favour periosteum over collagen membranes.

This reciprocal arrangement between the periosteum and chondrocytes suggested by Lindahl has not been supported by studies using alternatives to the periosteal flap. Bentley et al [89] reported comparable results using a biodegradable type I/III collagen membrane rather than periosteum to contain the chondrocytes within the defect. In this study 46 patients had autologous chondrocyte implantation with a type I/III collagen membrane and the remaining 12 patients had a periosteum cover as part of a prospectively randomized study comparing ACI with mosaicplasty. The mean age of the patients was 31.6 years and the mean defect size was 4.66 cm^2. Of the 58 patients treated with ACI, 51 (88%) had a good or excellent result. The mean follow up was 19 months. This confirmed that comparable results could be obtained using a type I/III biodegradable membrane rather than periosteum and favoured the hypothesis that the membrane/periosteum acts purely as a watertight seal.

There have been also some concerns about certain aspects of autologous chondrocyte implantation with a periosteum cover [159]. They included the co-morbidity associated with the longer incision required for the harvesting of the patch of periosteum and hypertrophy attributed to the periosteum which required shaving [89].

In this study there was a significant improvement in the modified Cincinnati score at 2 years following the ACI technique with a periosteum cover ($p<0.005$) and the ACI technique with a type I/III collagen membrane ($p<0.005$). There was a 49% improvement in the modified Cincinnati score at 2 years for the collagen covered

ACI group compared with a 38% improvement for the periosteum covered ACI. Of the 35 patients with defects treated by the ACI-collagen technique, 26 (74%) had a good or excellent result compared with 22 of 33 (67%) patients treated by ACI with a periosteum cover. There was no statistically significant difference between the 2 groups at 2 years based on the modified Cincinnati score (p value = 0.367) although there was trend for the ACI-collagen group to perform better based on the 95% confidence interval of the difference of the means.

The results from this prospective, randomized controlled trial would support the conclusions reached by Bentley et al [89] that a periosteum cover is not essential for the development and maturation of a hyaline repair following ACI. There was a tendency for the collagen covered ACI technique to result in a better outcome however this was not a significant finding with the numbers available, also this may have been due to a possible confounding factor in our study. As mentioned in the results more patients who had the periosteum covered technique had defects located over the patella than the collagen covered technique. Overall, 61% of the periosteum covered ACI group had patellar defects compared with 20% for the collagen covered group. However, of the patellar defects treated with the collagen covered ACI 86% reported a good or excellent result at 2 years although there were only 7 patients in this group. Out of the 20 patients with defects over the patella treated with the periosteum covered technique, 60% reported a good or excellent result. Comparing the patients who had defects over the medial femoral condyle, of the 8 patients treated with the periosteum covered ACI, 62.5% reported a good or excellent result which compared with 72% for the collagen covered ACI patients (18 patients in total). Clearly the ideal prospective, randomized study is a

study in which all the possible confounding factors have been standardized and the only variable is the one that you are assessing. However, in practical terms this is difficult to achieve since to standardize for age, sex, number of operations preceding chondrocyte implantation, duration of symptoms, aetiology of defect as well as location of the defect to name but a few is a near-impossible task. Possibly a larger study would have reduced the impact of this confounding factor, however in the light of the number of cases of graft hypertrophy following the periosteum covered technique it was felt inappropriate to continue randomizing patients to this technique and so the study was stopped. However, the results presented here do suggest that the techniques are at least comparable in terms of clinical outcome.

Peterson et al [72] reported on 61 patients who underwent an autologous chondrocyte implantation with a periosteum cover for isolated cartilage defects on the femoral condyle or the patella with a mean follow up of 7.4 years. At 2 years 51 (81.96%) of the 61 patients had a good or excellent result. This compares with our results of 74% good or excellent at 2 years for the ACI-collagen technique and 67% for the ACI-periosteum technique. This difference in outcome following ACI may be explained by the fact that the defects we operated on were bigger (mean defect size 4.54cm^2) and patients had a longer duration of symptoms (mean duration of symptoms 7.09 years compared with 3.4 years for patients with femoral condylar defects in Peterson's report) and had undergone more operations on their knees before the chondrocyte implantation (a mean of 2.09 operations compared with 1.5). In view of these differences it is difficult to make a direct comparison between our results and those of Peterson et al [72].

Arthroscopic examination at 1 year revealed remarkably similar results for both techniques, with the ACI-periosteum technique having 81% good or excellent results and ACI-collagen showing 79% good or excellent results based on the ICRS grading system.

At 1 year 13 patients in the ACI-collagen group and 14 patients in the ACI-periosteum group had biopsies of their grafts taken at arthroscopy. This showed that 9 (69.2%) out of 13 had a hyaline or mixed hyaline and fibrocartilage repair following the ACI-collagen technique compared with 6 (42.8%) out of 14 following the ACI-periosteum technique. This is encouraging for the ACI-collagen technique but the numbers are too small to be statistically significant.

Although there were considerable similarities in terms of the clinical result and arthroscopic assessment of the cartilage repair following these 2 techniques there were marked differences in terms of complications in the first 2 years following surgery. Within the first year 4 (12.1%) out of the 33 patients who had the ACI-periosteum technique required an unplanned arthroscopy for graft hypertrophy and shaving of the graft, this compared with 1 (2.9%) for the ACI-collagen group. At the 1 year check arthroscopy 12 (36.4%) patients who had the ACI-periosteum technique required shaving of hypertrophied grafts whereas no patients in the ACI-collagen group had this problem. At 18 months, 1 patient who had previously had their graft shaved and who had an ACI-periosteum repair required an unplanned arthroscopy for graft hypertrophy. One patient who had the ACI-collagen technique required an unplanned arthroscopy for graft hypertrophy within the second year following surgery and 1 patient had some graft hypertrophy at the 2 year repeat arthroscopy. Patients who developed this problem presented to the review clinic complaining of 'crunching' and 'grinding' from within the knee associated with pain

and catching as the knee flexed. In all cases their symptoms were relieved following an arthroscopy and shaving of the hypertrophied graft.

The high number of grafts that hypertrophied following the ACI-periosteum technique may be due to the fact that of the 33 patients who had this technique 20 (61%) had repairs to defects over the patella. However, this is an area of the knee where the articular cartilage is at its thickest and so problems of incomplete filling of the defect would be expected rather than 'overfilling'.

This is the first study to compare these 2 techniques of autologous chondrocyte implantation. From this study it can be concluded that the ACI-collagen technique compares favorably with the ACI-periosteum technique at 2 years. The only long-term follow-up in the published literature at present is for the ACI-periosteum technique [91]. Longer follow-up is needed to see if the ACI-collagen technique can also stand the test of time.

In summary, this study suggests that the results or the collagen covered ACI and the periosteum covered ACI are comparable based on clinical outcome and arthroscopic assessment at 2 years. However, the most striking feature seen in our review was the high incidence of graft hypertrophy in the periosteum-covered group which caused considerable morbidity, resulting in additional surgery in 6 patients (18%).

CHAPTER 6:

THE PRELIMINARY RESULTS OF THE MACI TECHNIQUE FOR THE TREATMENT OF OSTEOCHONDAL DEFECTS OF THE KNEE

Introduction

The results following the treatment of osteochondral defects in the knee with the autologous chondrocyte implantation technique have been encouraging as can be seen form the previous chapters and from the literature [36;72;89;91;153;156]. However, there have been some concerns about certain aspects of autologous chondrocyte implantation with a periosteum or collagen cover [159;162]. Such reservations include the potential for further surgical injury caused by the excision of a periosteal flap and the morbidity associated with a longer surgical incision needed to excise the periosteal flap and secure it to the rim of the osteochondral defect, possible damage to the recipient articular cartilage associated with the sutures used to fix the flap or membrane and the unequal distribution of chondrocytes after injection with the possibility of leakage of the chondrocyte suspension from beneath the flap or cover. With these reservations in mind a new technique of implanting the chondrocytes into a defect has been evolved. The Matrix carried Autologous Chondrocyte implantation (MACI; Verigen, Leverkusen, Germany) technique uses a porcine derived type I/III collagen membrane. One surface is smooth and represents the articular surface. On the reverse the surface is coarse which is due to large gaps between the collagen fibres which can be seen at a microscopic level. The chondrocytes are able to anchor themselves to the collagen fibres and form multiple layers on the coarse surface of the membrane. The method of implanting the membrane is more straightforward than that described for the ACI technique (involving no sutures and 'Tisseel' glue for fixation of the membrane)

and is quicker as a result, allowing for a shorter general anaesthetic time as well as tourniquet time. Also, the distribution of implanted cells in the defect is uniform although the number of cells implanted may be 2 or 3 times less than with injected cells.

Initial reports of the technique have been encouraging. Cherubino et al, showed that 6 patients with a minimum follow up of 6 months had an improvement in clinical and functional status after surgery [168].

The aim of this study was to review the 1 year results of the MACI technique in the first 107 patients at a single specialist centre. This represents the largest review at 1 year of this technique.

Patients and Methods

The South East Multi-Centre Research Ethics Committee and The Joint Research and Ethical Committee of the Royal National Orthopaedic Hospital Trust gave its approval before commencing this study (G. Bentley 2002 – personal communication).

A total of 107 patients with a mean age of 35 years (range 17 to 73.3 years) with symptomatic articular cartilage defects of the knee underwent the MACI technique. There were 64 men and 43 women. The mean defect size was 4.4 cm^2 (range 1 to 15.75 cm^2) with 54 having defects in the right knee and 53 in the left. Of the 107 patients, 54 defects were on the medial femoral condyle, 29 on the patella (21, single facet and 8 multiple facets), 12 on the lateral femoral condyle and 2 on the trochlea, 10 patients had multiple defects (table XXXVI). The aetiology of the lesions included 61 (57%) patients who had post traumatic defects, 16 (15%) patients had chondromalacia patellae, 6 (5.6%) had osteochondritis dissecans, 4

(3.7%) patients who had previous cartilage resurfacing techniques which had failed, 1 (0.9%) patient who had evidence of early osteoarthritis and 19 (17.8%) patients who had defects of unknown aetiology, although they were most probably post-traumatic (table XXXVII).

The mean duration of symptoms was 6.1 years (range 9 months to 38 years) and all patients except 1 had undergone a previous arthroscopy, the mean number of further operations was 2.15 (range 0 to 9). All patients were followed up at 12 months.

Not all patients had a straightforward MACI technique, 5 had a combined MACI and anterior cruciate ligament reconstruction (ACL) reconstruction (4 using a hamstring graft and 1using a bone-patellar tendon-bone graft), 3 had a MACI sandwich technique since they had defects that had a depth of more than 1 cm, 1 had microfracturing of an additional defect on the tibial plateau, 1 had a lateral release, 1 had a combined high tibial osteotomy, 1 had drilling of a trochlea defect and 1 patient required a bone graft to the base of the defect before the implantation was performed.

ANATOMICAL DISTRIBUTION	NUMBERS OF PATIENTS
Medial femoral condyle (MFC)	54 *(50%)*
Lateral Femoral Condyle (LFC)	12 *(11%)*
Patella-single facet	21 *(20%)*
Patella-multi facet	8 *(7%)*
Trochlea (Troch)	2 *(2%)*
MFC x 2	2 *(2%)*
MFC + LFC	1 *(1%)*
Patella + LFC	1 *(1%)*
Troch + MFC	1 *(1%)*
Patella + Trochlea	3 *(3%)*
Patella-multi facet + Troch	1 *(1%)*
Patella (med + lat) + Troch x 3	1 *(1%)*
Total	**107*(100%)***

Table XXXVI. Anatomical site of the defects found in 107 patients before undergoing the MACI technique, by number and *percentage.*

AETIOLOGY OF DEFECTS	NUMBERS OF PATIENTS
Trauma	62 *(57.9%)*
Osteochondritis dissecans	6 *(5.6%)*
Chondromalacia patellae	16 *(15%)*
Previously failed cartilage resurfacing technique	4 *(3.7%)*
Other	19 *(17.8%)*
Total	**107 *(100%)***

Table XXXVII. Aetiology of the defects found in 107 patients undergoing the MACI technique, by number and *percentage.*

The indication for surgery in all cases was pain associated with a chondral or osteochondral defect. Other symptoms included swelling, giving way, catching and locking.

Surgical Technique

The procedure was divided into 2 stages. An arthroscopy was carried out initially together with an examination under anaesthesia to assess the stability of the knee. If the defect was suitable for chondrocyte implantation, a full thickness cartilage biopsy of approximately 300-500 mg was harvested from the margin of the trochlea of the damaged knee using a gouge. The specimen was then removed from the knee via one of the arthroscopy portals. The cartilage biopsy was then put into a sterile container and transferred to the laboratory. The specimen was enzymatically digested releasing the chondrocytes, which were then grown in a monolayer culture.

The patient was readmitted 3 to 5 weeks later and the second stage of the procedure was performed. To ensure a bloodless field a tourniquet was applied and a medial or lateral parapatellar arthrotomy was performed depending on the location of the defect. Intravenous antibiotics (1g of flucloxacillin and 1g of amoxycillin) were administered over the peri-operative period as prophylaxis against infection. Once the defect was identified it was debrided back to a stable rim of normal cartilage with a scalpel to minimize cartilage trauma. The base of the defect was also debrided of old cartilage down to the subchondral bone, taking care to avoid bleeding. If bleeding did occur this was controlled by pressure on the bone with a gauze swab soaked in 1 in 200,000 Adrenaline.

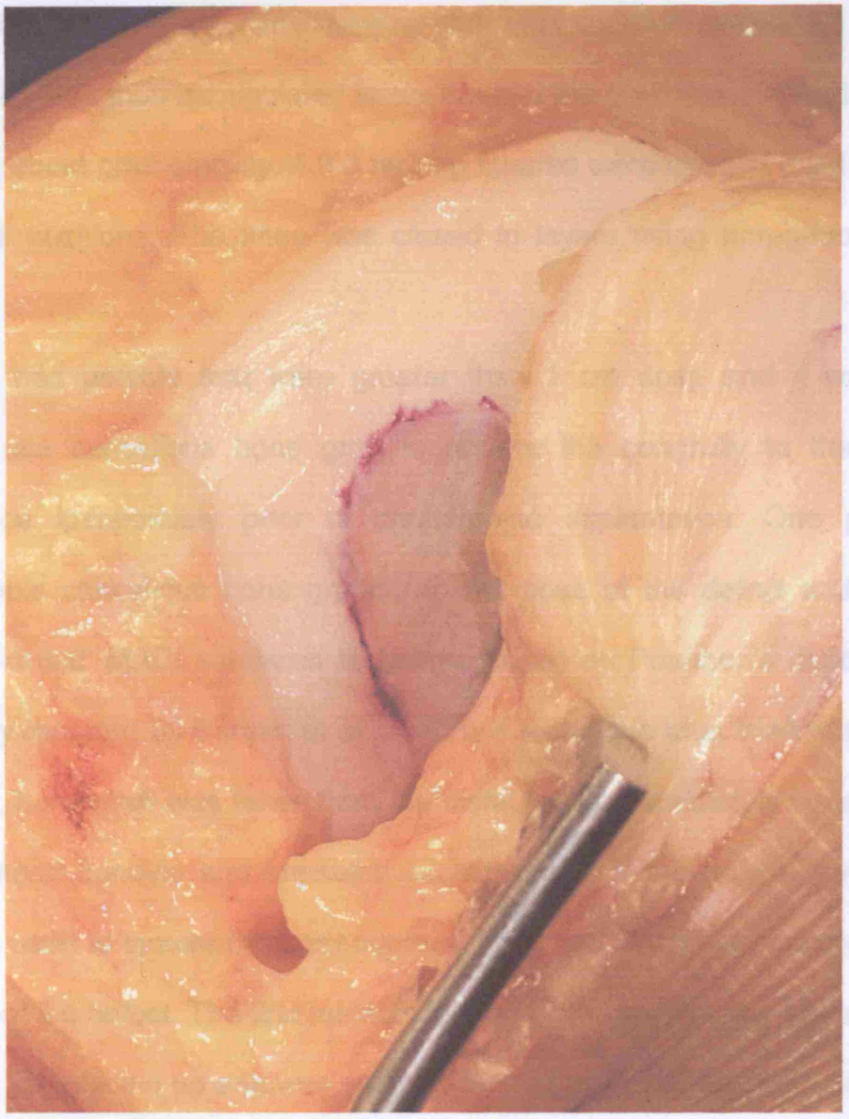

Figure XXVI. Photograph showing a MACI repair of an osteochondral defect over the medial femoral condyle employing tissue glue rather than sutures to secure the membrane to the defect.

Once the defect had been prepared the membrane carrying the cells (0.5-1 million/cm^2) was cut to size and secured using fibrin glue to the base of the defect with the cells facing down. Firm pressure was applied to the graft for approximately 3 minutes whilst the glue set, any excess glue was carefully removed (figure XXVI). The knee was then manipulated to ensure that the graft was stable. If there were concerns about graft stability, 4 6'0 tacking sutures were used at the 12, 3, 6 and 9 '0' clock positions. The knee was closed in layers using non-absorbable sutures.

Four patients had defects that were greater than 1 cm deep and it was felt necessary to use cancellous bone graft to restore the congruity to the bony articular surface immediately prior to chondrocyte implantation. One patient underwent simple cancellous bone grafting to the base of the defect and three required a 'so-called' MACI sandwich technique based on Peterson's description [165] and recently reported by Bartlett et al [169]. In this technique after the defect had been debrided, bone graft was taken from the distal femur immediately superior to the medial femoral condyle and impacted into the base of the defect. Sufficient bone graft was used to restore the bony contour. Then two MACI membranes were cut to the size of the defect. The first membrane was implanted into the base of the defect with the cells facing up and was secured to the base of the defect with fibrin glue. The second MACI membrane was implanted on top of the first membrane with the cells facing down and again secured with fibrin glue. Light digital pressure was applied to the graft for 3 minutes whilst the glue set. The knee was then closed using non-absorbable sutures.

Five patients with a confirmed ruptured anterior cruciate ligament at arthroscopy, as well as an osteochondral defect and who complained of pain and instability had an anterior cruciate ligament reconstruction as well as a MACI repair. This was

performed before implantation during the same operative procedure. In 4 cases a hamstring reconstruction and in 1 case a bone-patellar tendon-bone graft was used which was routed through standard tibial and femoral tunnels. Femoral fixation was achieved through a separate lateral incision with the anchoring sutures attached over a biodegradable post. The tibial fixation was secured using a biodegradable screw. Under the same general anaesthetic the MACI procedure was performed as described. One patient had a varus malalignment, which was corrected with a lateral closing wedge high tibial osteotomy, which was performed before implantation under the same general anaesthetic.

Rehabilitation

The patients who had the MACI technique only, followed the same course of rehabilitation as previously described for the ACI-P and ACI-C techniques (page 108-109).

The 5 patients who had an ACL repair as well as a chondrocyte implantation were rehabilitated in the immediate post-operative period on a continuous passive motion machine and were discharged once they achieved 90° of flexion. In the case of the patient who had a combined osteotomy and MACI, he was rehabilitated in a knee brace, which was locked in extension and was allowed to partially weight-bear for the first two weeks. At this stage the brace was unlocked and the patient was allowed to continue partially weight bearing for a further 4 weeks. At 6 weeks after surgery the brace was removed and the patient was allowed to gradually increase the weight put through the leg as comfort allowed. Further rehabilitation focused on improving the patients' range of movement and muscle strengthening exercises.

Evaluation

Patients were evaluated clinically and arthroscopically as described on pages 109-111.

Statistical analysis. Statistical comparison of the clinical assessment scores at 1 year was by the paired Students T test. Comparisons between the good and excellent group and fair and poor group were made using the unpaired Student T test. A p value of less than 0.05 was considered statistically significant.

Results

Clinical review

The pre-operative modified Cincinnati rating system scores are shown in table XXXVIII, 34 (32%) had a good score, 54 (50%) had a fair score and 19 (18%) had a poor score. Those 34 patients with a good score were nevertheless considered suitable for a MACI because they complained of considerable pain on exertion that was attributed to an articular cartilage defect. All these patients functioned at a high level so that despite scoring badly for pain they were able to compensate on the remaining parameters of the modified Cincinnati score, which in this situation tends to give a misleading impression of their symptomatology.

The mean modified Cincinnati knee score improved from 45 pre operatively to 64 post operatively at 1 year (difference of the means 18, with a 95% confidence interval that the difference of the means lies between 17.20 and 19.38, $p<0.005$), representing a 42% increase. Of the 107 patients, 74 (69%) had a good or excellent result (table XXXIX).

TOTAL	EXCELLENT	GOOD	FAIR	POOR
107		34 *(32%)*	54 *(50%)*	19 *(18%)*

Table XXXVIII. Modified Cincinnati scores before undergoing the MACI technique.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
107	30 *(28%)*	44 *(41%)*	26 *(24%)*	7 *(7%)*

Table XXXIX. Modified Cincinnati scores following the MACI technique at 1 year.

ANATOMICAL DISTRIBUTION	TOTAL	EXCELLENT	GOOD	FAIR	POOR
Medial femoral condyle	54	14 *(26%)*	19 *(35%)*	17 *(32%)*	4 *(7%)*
Lateral femoral condyle	12	6 *(50%)*	5 *(42%)*	1 *(8%)*	
Patella-single facet	21	5 *(23.8%)*	10 *(47.6%)*	4 *(19%)*	2 *(9.5%)*
Patella-multiple facet	8	2 *(25%)*	3 *(37.5%)*	2 *(25%)*	1 *(12.5%)*
Trochlea	2		1 *(50%)*	1 *(50%)*	
Multiple defects	10	2 *(20%)*	6 *(60%)*	2 *(20%)*	

Table XL. Clinical results at 1 year for 107 patients who had a MACI for chondral or osteochondral defects of the knee by number and *percentage*.

Table XL shows that at 1 year of the 54 patients with defects over the medial femoral condyle treated by MACI, 33 (61%) had a good or excellent result. For the lesions of the lateral femoral condyle 11 (92%) out of 12 patients reported good or excellent results. For patellar lesions, 20 (69%) out of 29 patients reported good or excellent results. Of the 10 patients who had multiple defects 8 (80%) reported a good or excellent results, the numbers of patients with trochlea defects were too small for any useful analysis.

Factors which affect outcome

A comparison was made between those patients in the good/excellent group and those in the fair/poor group. Table XLI shows the differences between these groups in terms of their age, defect size, duration of symptoms leading up to surgery and number of surgical procedures before chondrocyte implantation.

The 74 patients with a good/excellent result at 1 year had an average age of 33.9 years compared with the 33 patients who had a fair or poor result who had an average age of 37.2 years, however this difference was not significant ($p=0.096$).

There was no significant difference between the good/excellent group and the fair/poor group in terms of defect size ($4.76cm^2$ vs $4.07cm^2$, $p=0.2$), duration of symptoms (6.06 years vs 5.97 years, $p=0.95$) or surgical procedures prior to implantation (2.2 vs 2.09, $p=0.78$).

	GOOD/ EXCELLENT	FAIR/ POOR	P VALUE
MEAN AGE (YRS)	33.9 (range 17-73.3)	37.2 (range 21-50.6)	0.096
MEAN DEFECT SIZE (CM^2)	4.76 (range 1-15.75)	4.07 (range 1-8.75)	0.2
MEAN DURATION OF SYMPTOMS (YRS)	6.06 (range 0.75-38)	5.97 (range 1.3-28)	0.95
PRE OPERATIVE SURGERY	2.2 (range 0-9)	2.09 (range 1-7)	0.78

Table XLI. Comparison between the Good/excellent group and the Fair/poor group following MACI technique.

Arthroscopic review

A total of 40 patients had a repeat arthroscopy and biopsy at 1 year following the chondrocyte implantation. The International Cartilage Repair Society Score (ICRS) was 1 (excellent) or 2 (good) in 32 of 40 patients (80%). The arthroscopy of 4 patients did not show any evidence of the graft and scored an ICRS of 4 and were recorded as graft failures (10%) (table XLII).

Of the biopsies taken at the time of the check arthroscopy, 2 were from the trochlea, 5 from the patella, 4 from the lateral femoral condyle and 29 from the medial femoral condyle. Hyaline cartilage (figure XXVII) was found in 6 patients (15%), which consisted of sparse, oval shaped cells, evenly distributed in lacunae enveloped within a matrix that stained positively for Safranin O. The biopsies of 9 patients (22.5%) showed a mixture of hyaline and fibrocartilage, that is the biopsy specimen contained more than 40% but less than 60% hyaline cartilage. Of the 40 biopsies, 25 (62.5%) had the appearance of fibrocartilage, which had a rather disorganised appearance and under polarised light, a meshwork of collagen fibrils could be seen throughout the specimen.

ICRS GRADE	NUMBER (%)
1, Excellent	18 *(45%)*
2, Good	14 *(35%)*
3, Fair	4 *(10%)*
4, Poor	4 *(10%)*
Total	40 *(100%)*

Table XLII. Arthroscopic results at 1 year for 40 patients following the MACI technique, by number and *percentage*.

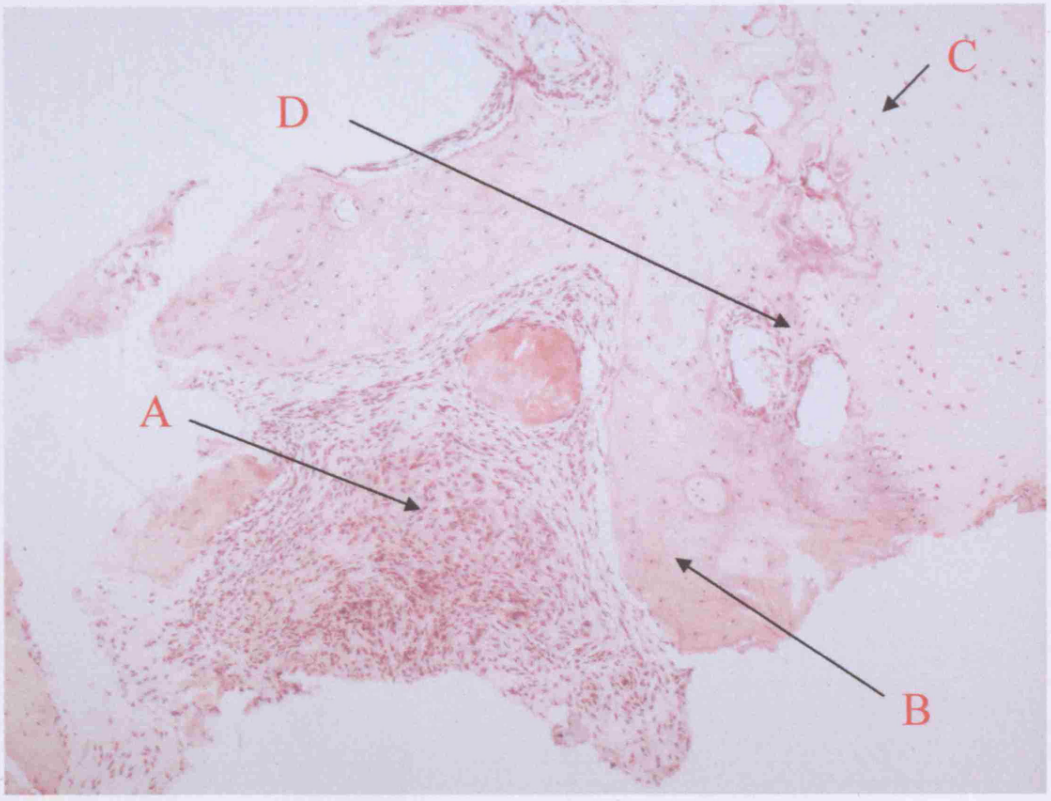

Figure XXVII. Photomicrograph of a full thickness biopsy of a MACI repair showing the interface of the cartilage repair and underlying bone. Hyaline like cartilage material, C is seen bonded to the underlying bone, B. The intact bone/cartilage interface is indicated, D. The underlying bone marrow is also indicated A. (Haematoxylin and eosin x 34). Patient number 264 (see Appendix III: Table of Results).

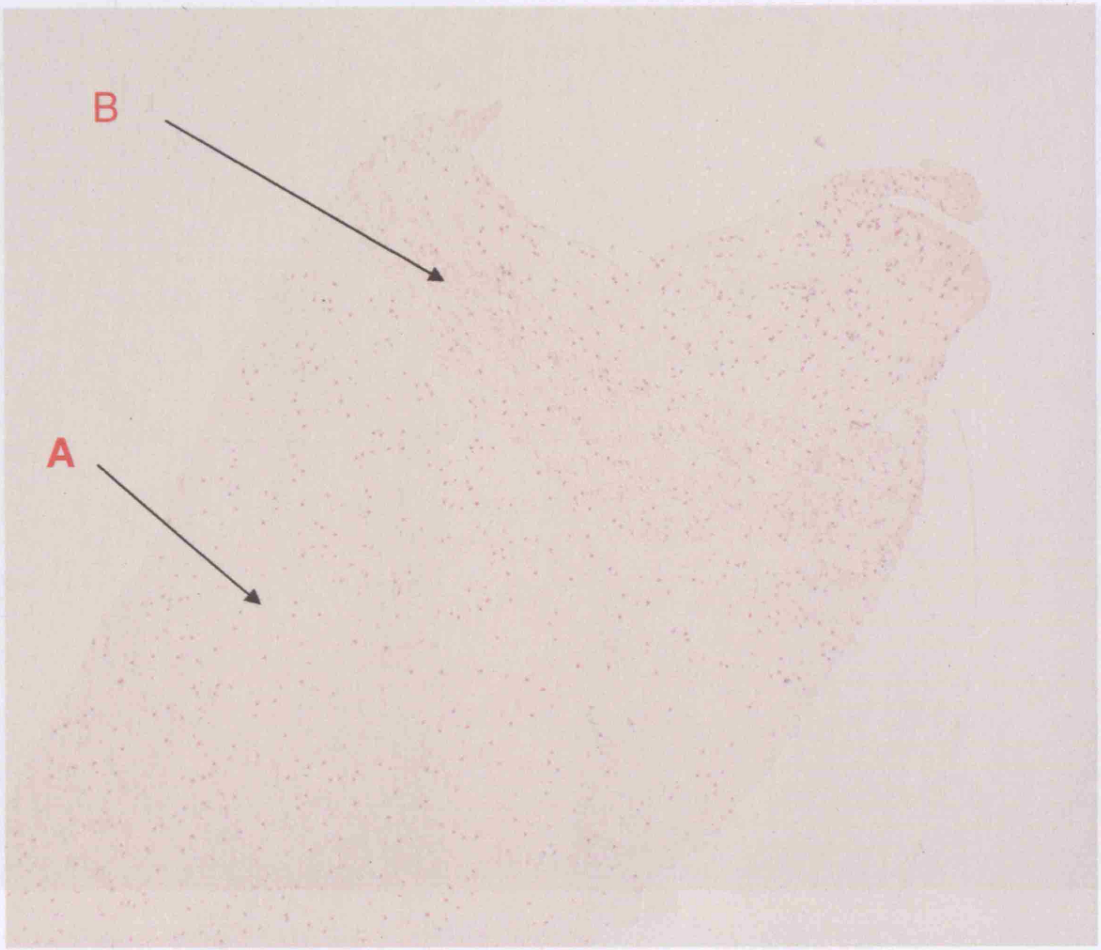

Figure XXVIII. Photomicrograph of a full thickness biopsy of a MACI repair showing the surface of the cartilage repair (same biopsy specimen as figure XXVII). Hyaline like cartilage material, A is seen with overlying fibrocartilage nearer the surface B (Haematoxylin and eosin x 3.4). Patient number 264 (see Appendix III: Table of Results).

Figure XXIX. Photomicrograph taken at high power of a full thickness biopsy of a MACI repair showing chondrocytes within lacunae embedded within a matrix which stains strongly for proteoglycan (Safranin O x 34). Patient number 249 (see Appendix III: Table of Results).

Complications

There were 5 non graft related and 18 graft related complications in this review (table XLIII). One patient developed an above knee deep vein thrombosis and was anticoagulated for 6 months with warfarin. One patient developed septic arthritis following harvesting which resolved following a washout and a course of antibiotics, this delayed the time of implantation for 2 weeks but there were no long term adverse sequelae as the graft successfully filled the defect and clinically the patient made an excellent recovery. Two patients developed a superficial wound infection which resolved with a course of antibiotics. One patient went into urinary retention post operatively and required a urinary catheter.

Three patients required an arthroscopy before the 1 year check. One patient required an arthroscopy and division of adhesions at 1 month following grafting to 5 defects. One patient developed a lateral meniscal tear that was debrided and the last patient complained of 'clunking' and so a diagnostic arthroscopy was carried out but no cause was found. Eight patients were slow to mobilise and required a manipulation under anaesthetic. Three patients complained of painful catching and a subsequent check arthroscopy at 1 year revealed that the grafts had hypertrophied. Their symptoms resolved following arthroscopic shaving of the grafts. Of the 40 patients who had a repeat arthroscopy at 1 year there were 4 cases of graft failure, although this represents 4% of the total patient population (4 out of 107 patients). The grafts in these cases were over the retropatellar surface.

COMPLICATION	NUMBER
MAJOR	
Septic arthritis following harvesting	1
Deep Vein Thrombosis	1
Graft failure	4
INTERMEDIATE	
Graft hypertrophy at 1 year	3
MINOR	
Urinary retention post operatively required urinary catheter	1
Superficial wound infection	2
Slow to mobilise requiring a manipulation under anaesthetic	8
Unplanned arthroscopy	3

Table XLIII. Complications in the first year following MACI in 107 patients.

Discussion

This is the largest current review of a relatively new technique for the treatment of symptomatic osteochondral defects of the knee. Our results have shown that the MACI technique can result in a significant improvement in the functional score at 1 year and of the 107 patients reviewed, 69% reported a good or excellent score. Out of a total of 40 repeat arthroscopies at 1 year, 36 showed good filling of the defect with bonding at the edges of the repair to the surrounding articular cartilage. Hyaline cartilage or mixed hyaline and fibrocartilage were present in 15 of 40 (37.5%) biopsies. A higher frequency of hyaline and mixed hyaline and fibrocartilage repairs have been reported in other studies [36;72;90;165]. As has previously been noted there is some evidence to suggest that cartilage repairs continue to mature after 1 year [89;91]. Therefore, more hyaline repairs could be expected if the biopsies were to be repeated at years 3 or 4.

Bentley et al reported 88% good or excellent results following the ACI technique with either a collagen or periosteum cover at a mean follow up of 19 months [89]. Possibly MACI grafts take longer to mature in comparison to the ACI-C and ACI-P techniques. They may take longer to mature since unlike the ACI-C or ACI-P techniques the base of the defect in the MACI technique is covered in a layer of fibrin glue to secure the membrane. As a result the chondrocytes have to diffuse through this fibrin layer to attach themselves to the subchondral bone. In the past there has been some controversy whether the chondrocytes are able to migrate through the fibrin glue at all [163]. More recently Zheng et al have shown in their studies [160] with the MACI membrane that chondrocytes are able to migrate from the membrane into the glue within 2 weeks. Willers et al [170] went on to conclude that the fibrin glue forms an integral component of the MACI membrane scaffold

and at the Combined Orthopaedic meeting in Sydney 2004, Zheng concluded that human chondrocytyes are able to express thrombin receptors on their surface and that fibrin-sealant is capable of inducing chondrocyte proliferation and migration [171]. However, unlike the collagen or periosteum covered techniques which ensure direct contact between the chondrocytes and the base of the defect, the layer of fibrin glue which secures the MACI membrane could act as a delaying factor for the successful development of a graft.

There were 4 cases where the graft had failed, 3 of these occurred in patients with defects over the retropatellar surface and 1 over the medial femoral condyle. In the case of the patella failures, this could well be due to a combination of factors including the thickness of native cartilage in this area of the joint and also due to the high loading forces that occur in the patellofemoral joint. In the recent report by Bartlett et al [172] there were no failures for the collagen covered technique(ACI-C) and Peterson reported 2 failures (total of 58 patients) following the periosteum covered technique (ACI-P) in his 2003 paper [165]. In our study, out of a total of 40 patients who had repeat arthroscopies there were 4 (10%) graft failures, although including patients who did not have a repeat arthroscopy, this represented 4% of the total (4 out of 107 patients).

The repairs to defects over the lateral femoral condyle were encouraging with 92% of patients reporting good or excellent results. Although only 12 patients were reviewed, these results are extremely encouraging for an area of the joint, which can be difficult to repair using the collagen or periosteum covered techniques. The results for repairs to the medial femoral condyle were not as good as those results reported by Bentley [89] and Peterson [72] with only 61% reporting good or excellent results. This could be due to delayed graft maturation as discussed above.

In this study there was no significant difference between the good/excellent and fair /poor group in terms of age, defect size, duration of symptoms leading up to surgery and number of surgical procedures before chondrocyte implantation. Perhaps these factors become more prevalent with longer follow up.

In summary, we have shown that the MACI technique can result in an improvement in patients' functional scores and can result in a hyaline repair. However, there are concerns about the relatively high rate of graft failure (10% of those arthroscoped at 1year) compared with other chondrocyte implantation techniques and the low frequency of hyaline repairs. Longer follow up may show more hyaline repairs as the grafts mature. For this technique to gain widespread recognition these issues need to be resolved.

CHAPTER 7:

PROGRESS OF A PROSPECTIVE, RANDOMISED STUDY COMPARING TWO TECHNIQUES OF AUTOLOGOUS CHONDROCYTE IMPLANTATION FOR OSTEOCHONDRAL DEFECTS IN THE KNEE: MACI vs ACI

Introduction

The Matrix associated autologous chondrocyte implantation technique or MACI attempts to address the concerns about certain aspects of autologous chondrocyte implantation with either a periosteum or collagen cover. The co-morbidity associated with harvesting of the periosteal flap, the unequal distribution of chondrocytes after injection and the placing of multiple sutures in the rim of healthy cartilage to anchor the cover, are but a few of these concerns. Following the encouraging results reported in the last chapter for the MACI technique, a prospectively, randomised study was established to compare the results following the MACI and collagen covered ACI techniques at 1 year.

Patients and Methods

The South East Multi-Centre Research Ethics Committee and The Joint Research and Ethical Committee of the Royal National Orthopaedic Hospital Trust gave its approval before commencing this study (G. Bentley 2002 – personal communication).

Between March and November 2002, a total of 52 patients with symptomatic articular cartilage defects were randomised to have either ACI with a type I/III porcine collagen cover (26 patients) or MACI (26 patients) technique. There were 29 men and 23 women with a mean age of 37.5 years (range 25 to 52 years) for

the ACI group and 31.72 years (range 20 to 46 years) for the MACI group. The mean defect size was 5.09 cm^2 (range 1.5 to 10.35 cm^2) for the ACI group and 4.66 cm^2 (range 1 to 16 cm^2) for the MACI group. This apparent difference in defect size was not statistically significant with a p value >0.05.

Of the 52 patients 31 had defects over the left knee and 21 over the right. Of the 26 patients in the ACI group 13 (50%) had defects over the medial femoral condyle, 2 (8%) over the lateral femoral condyle, 10 (38%) over the patella (5 single facet and 5 multi-facet) and 1 over the trochlea (4%). Of the 26 patients in the MACI group 10 (38%) had defects over the medial femoral condyle, 2 (8%) over the lateral femoral condyle, 10 (38%) over the patella (6 single facet and 4 multi-facet), 1 (4%) over the trochlea, 1 (4%) patient with a defect over the patella and a further defect over the trochlea, 1 (4%) patient with 2 defects over the medial femoral condyle and 1(4%) patient with 5 defects, 2 over the patella and 3 over the trochlea (table XLIV).

The aetiology of the lesions for the ACI group included 8 (30.8%) who had post-traumatic defects, 2 (7.7%) who had osteochondritis dissecans, 6 (23.1%) who had chondromalacia patellae, 7 (26.9%) who had a previous failed Matrix support prosthesis (MSP) or Mosaicplasty or ACI and 3 (11.5%) who had defects of unknown aetiology, although were most probably post-traumatic. Thirteen (50%) of the MACI group had post-traumatic defects, 1 (4%) had osteochondritis dissecans, 6 (23%) had chondromalacia patellae, 1 (4%) had early osteoarthritis, 1(4%) had a previously failed MSP and 4 (15%) had defects of unknown aetiology (table XLV).

The mean duration of symptoms was 9.6 years (range 1 to 38 years) and all patients had undergone a previous arthroscopy, the mean number of further operations was 2.3 (range 1 to 7). All patients were followed up at 12 months.

The indication for surgery in all cases was disabling pain associated with a chondral or osteochondral defect. Other symptoms included swelling, giving way, catching and locking.

ANATOMICAL DISTIBUTION			
	TOTAL	ACI	MACI
Medial femoral condyle	23	13 *(50%)*	10 *(38%)*
Lateral femoral condyle	4	2 *(8%)*	2 *(8%)*
Patella (single facet)	11	5 *(19%)*	6 *(23%)*
Patella multi-facet)	9	5 *(19%)*	4 *(15%)*
Trochlea	2	1 *(4%)*	1 *(4%)*
Patella + Trochlea	1		1 *(4%)*
Patella (medial and lateral facet) + trochlea x 3	1		1 *(4%)*
Medial femoral condyle x 2	1		1 *(4%)*
Total	**52 *(100%)***	**26 *(100%)***	**26 *(100%)***

Table XLIV. Anatomical site of the defects found in 52 patients, by number and *percentage*, for the MACI vs ACI-C study.

AETIOLOGY OF DEFECTS			
	TOTAL	ACI	MACI
Trauma	21	8 *(30.8%)*	13 *(50%)*
Osteochondritis dissecans	3	2 *(7.7%)*	1 *(4%)*
Chondromalacia patellae	12	6 *(23.1%)*	6 *(23%)*
Early osteoarthritis	1		1 *(4%)*
Previous failed MSP/Mosaicplasty/ACI	8	7 *(26.9%)*	1 *(4%)*
Other	7	3 *(11.5%)*	4 *(15%)*
Total	**52 *(100%)***	**26 *(100%)***	**26 *(100%)***

Table XLV. Aetiology of the defects found in 52 patients, by number and *percentage*, for the MACI vs ACI-C study.

Surgical Technique

The surgical technique for the ACI-C and the MACI procedure has already been described (ACI-C pages 140-141 and MACI pages 203-206).

Patients were randomised using random sample numbers in sealed envelopes.

Rehabilitation

The rehabilitation programme was identical after both techniques and followed the same course as previously described page 108-109.

Evaluation

Patients were reviewed in the Orthopaedic Clinic at regular intervals up to 1 year. One Observer, who did not perform any of the implantations, independently reviewed the patients. Patients were evaluated clinically and arthroscopically as described on pages 109-111.

Statistical analysis. Statistical comparison of the pre-operative and postoperative clinical assessment scores at 1 year for each of the techniques and a comparison of the outcome scores between the groups, was by the paired Students T test. A p value of less than 0.05 was considered statistically significant.

Results

Clinical Review

The pre-operative modified Cincinnati rating system scores are shown in table XLVI for both techniques. Out of a total of 26 patients who had the ACI technique, 4 (15%) had a good score, 15 (58%) had a fair score and 7 (27%) had a poor score pre-operatively. Out of a total of 26 patients who had the MACI technique 5 (19%) had a good score, 18 (69%) had a fair score and 3 (12%) had a poor score pre-operatively. Those patients that had a good score were nevertheless considered suitable for chondrocyte implantation because they complained of considerable pain particularly on exertion that was attributed to their cartilage defects. All these patients were athletic and were able to function at a high level and so were able to compensate for the poor pain score with the other parameters on the modified Cincinnati rating system. The mean modified Cincinnati score at 1 year for the patients who underwent the MACI technique was 59 (n=26) and for the ACI technique was 49 (n=26), to give a difference of the means of 10 (with a 95% confidence interval that the true difference of the means lies between 5.37 and 24.37, $p=0.2$)

There was a significant improvement in the modified Cincinnati score at 1 year following the MACI technique ($p<0.05$). However the group of patients who had previous extensive cartilage repairs such as MSP or mosaicplasty adversely affected the ACI results. Not including this subgroup, there was also a significant improvement in clinical outcome at 1 year ($p<0.05$).

Overall, of the 26 patients with defects treated by the ACI technique, 12 (46%) had a good or excellent result (table XLVII) compared with 16 of 26 (62%) patients treated by the MACI technique.

ACI	TOTAL	EXCELLENT	GOOD	FAIR	POOR
	26	0	4	15	7

MACI	TOTAL	EXCELLENT	GOOD	FAIR	POOR
	26	0	5	18	3

Table XLVI. Modified Cincinnati scores before surgery, for the MACI vs ACI-C study.

ACI	TOTAL	EXCELLENT	GOOD	FAIR	POOR
	26	3	9	7	7

MACI	TOTAL	EXCELLENT	GOOD	FAIR	POOR
	26	7	9	5	5

Table XLVII. Modified Cincinnati scores at 1 year following the ACI-C and MACI technique.

Table XLVIII shows the results at 1 year based on the site of the defect. Of the 13 defects over the medial femoral condyle treated with the ACI technique, 4 (31%) had a good or excellent result compared with 6 (60%) out of 10 treated by the MACI technique ($p>0.05$). Of the 13 patients with MFC defects treated with the ACI technique 6 had previous extensive cartilage repairs (either with MSP or Mosaicplasty), which adversely affected the results.

In the case of defects over the patella, 6 (60%) out of 10 had a good or excellent result following the ACI technique compared with 5 (50%) out of 10 for the MACI technique ($p>0.05$).

The numbers of defects of the lateral femoral condyle, trochlea and multiple defects were too small for statistical analysis.

These results show that there is no statistically significant difference between the ACI and MACI technique in terms of clinical outcome at 1 year.

ANATOMICAL DISTRIBUTION	TOTAL	EXCELLENT	GOOD	FAIR	POOR	P VALUE
MFC						
ACI	13		4	4	5	p>0.05
MACI	10	2	4	2	2	
LFC						
ACI	2		1		1	Sample
MACI	2	2				too small
Patella						
ACI	10	2	4	3	1	p>0.05
MACI	10	2	3	2	3	
Trochlea						
ACI	1	1				Sample
MACI	1			1		too small
Multiple						
ACI						Sample
MACI	3	1	2			too small

Table XLVIII. Clinical results at 1 year for 52 patients who had either an ACI or a MACI for osteochondral defects of the knee.

Arthroscopic Review

A repeat arthroscopy was made at the 1 year mark following the chondrocyte implantation. Of the 26 patients who had the ACI technique, 9 had a repeat arthroscopy at 1 year (table XLIX). All 9 patients had an ICRS grade of 1 or 2 compared with 8 (80%) out of 10 who had the MACI technique. Unfortunately, at the time of this review 33 patients were awaiting a repeat arthroscopy at 1 year, resulting in the small numbers.

ICRS GRADE	ACI	MACI
	1 YEAR	1 YEAR
1, Excellent	1	2
2, Good	8	6
3, Fair		1
4, Poor		1
Total	9	10

Table XLIX. Arthroscopic results at 1 year for patients who had either the ACI or MACI technique.

Complications

Within the first year following chondrocyte implantation there was just one case of graft failure in the case of a MACI patient who had a defect over the patella, otherwise the rest of the complications were minor (table L). There were 4 patients in each group who had graft hypertrophy requiring shaving at 1 year. Three patients in the ACI group were slow to mobilise (unable to flex to 90° at 6 weeks) and required a manipulation under anaesthetic compared with 2 in the ACI group and there were 3 patients in each group who required unplanned arthroscopies for adhesions.

COMPLICATION	NUMBER	
	ACI	MACI
MAJOR		
Graft failure		1
INTERMEDIATE		
Graft hypertrophy	4	4
MINOR		
Urinary retention post-operatively requiring a catheter		1
Large plica removed at repeat arthroscopy	1	
Reflex sympathetic dystrophy		1
Slow to mobilize requiring a manipulation under anaesthetic	3	2
Unplanned arthroscopy division of adhesions meniscal tear ? infection	 1 1 1	 2 1

Table L. Complications within the first year following the ACI and MACI technique.

Discussion

Brittberg's original technique of autologous chondrocyte implantation uses a chondrocyte suspension, which is injected into a cartilage defect underneath a periosteum cover. Because of concerns of graft hypertrophy and also possible morbidity associated with harvesting of periosteum alternatives were sought to the periosteum cover. Considerable success has been achieved with a porcine type I/III collagen cover as an alternative to periosteum. However, even with this technique there have been some misgivings. These include possible damage to the cartilage at the rim of the defect to which the collagen membrane is sutured; there is also the possibility that the chondrocyte suspension may leak out from underneath the membrane. Other concerns include the uneven distribution of the chondrocyte suspension over the cartilage defect. To address these issues the MACI technique evolved. With this technique the chondrocytes are applied evenly over a collagen membrane and the membrane is glued to the base of the defect with fibrin glue. This technique avoids the use of sutures and any possible damage to the cartilage at the rim of the defect. However, at the time of writing there are no studies that have compared the ACI and MACI techniques.

The results of the ACI group in this study were heavily influenced by a group of patients who had 'revision' cartilage resurfacing techniques. The 7 patients who had a previous mosaicplasty or matrix support prosthesis which were subsequently revised using the ACI-collagen technique did not do well, resulting in just 46% good or excellent results in this group as a whole. This compared with 62% treated by the MACI technique. Excluding the 7 patients who had repeat cartilage resurfacing, there was no statistically significant difference between the 2 groups in

terms of clinical outcome. In terms of arthroscopic findings at 1 year following the chondrocyte implantation there was no difference in macroscopic appearance, however the numbers were small.

The number of complications encountered following both techniques was essentially the same with both techniques having similar numbers of graft hypertrophy, unplanned arthroscopies and patients who were slow to mobilize requiring an MUA.

It is interesting to compare these results with those of Peterson et al in their paper of 2002 [72]. Peterson reported on 19 patients who had repairs to defects over the femoral condyle using the ACI-periosteum technique. Eighty-nine percent of patients reported good or excellent results at 2 years with a mean defect size of 3.4 cm^2 and a mean duration of symptoms of 3.4 years. In our study 15 patients had the ACI-collagen technique to the femoral condyles, 33% reported good or excellent results. Patients that had a previous mosaicplasty or MSP to the same defect adversely affected these results. The mean defect size for this group was 4.84 cm^2 and the mean duration of symptoms was 12.5 years. Of the MACI group who had repairs to the femoral condyle, 67% reported good or excellent results at 1 year. The mean defect size for this group was 4.22 cm^2 and the mean duration of symptoms was 11 years.

Peterson reported on 17 patents who had defects over the patella with 65% reporting good or excellent results with a mean defect size of 4.4 cm^2 and a mean duration of symptoms of 7.2 years. In our study 10 patients with patella defects had the ACI-collagen technique with 60% reporting good or excellent results with a mean defect size of 3.54 cm^2 and a mean duration of symptoms of 9.8 years. Ten patients in the MACI group had defects repaired over the patella with 50%

reporting good or excellent results with a mean defect size of 5.31 cm^2 and a mean duration of symptoms of 5.4 years.

These results would suggest that the periosteum covered ACI technique is superior to both MACI and the ACI-collagen technique particularly for femoral condylar defects. However, Petersons' patients have on average smaller defects and a shorter duration of symptoms and also all our patients were reviewed at 1 year as apposed to 2 years as in Petersons' study.

The preliminary results of this prospectively randomized study did not show a statistically significant difference between the 2 techniques in terms of clinical outcome at 1 year. There did not appear to be a difference between the grafts arthroscopically at 1 year, although only a small number of patients had a repeat arthroscopy by the time of this review.

CHAPTER 8:

CHONDROCYTE IMPLANTATION IN THE KNEE COMBINED WITH OTHER SURGICAL PROCEDURES

Introduction

Minas and Nehrer [122] reported in their review that any tibiofemoral malalignment or ligamentous instability or bone insufficiency must be managed prior to, or at the time of cartilage repair. Rupture or laxity of the anterior cruciate ligament can result in abnormal translation and rotation of the femur on the tibia resulting in shearing of the chondrocyte graft and failure of the repair.

If limb malalignment is not corrected prior to or at the time of the chondrocyte implantation excessive loading on the repair may result in early graft failure. Brittberg et al [153] went on to suggest that patients with large defects who do not have major malalignment may benefit from either an unloader brace or even an unloading osteotomy. They suggested that repairs that are not protected may have a good appearance at 2 years but high loads on the repair area may cause progressive thinning of the matrix that ultimately leads to destruction of the graft. At present however, osteotomies are reserved for patients who have a significant valgus or varus malalignment.

Repairs to lesions up to 8mm in depth are stated to achieve a good clinical result after autologous chondrocyte implantation alone [72]. However, Brittberg et al have recommended that bone grafting is required for defects of more than 8 to 10 mm in depth to restore the bony contour of the articular surface.

Following the encouraging results of these combined techniques [91;165], this study reports on 12 patients who had a chondrocyte implantation combined with another reconstructive surgical procedure aimed restore the biomechanics of the joint to normal or near-normal.

Patients and Methods

The South East Multi-Centre Research Ethics Committee and The Joint Research and Ethical Committee of the Royal National Orthopaedic Hospital Trust gave its approval before commencing this study (G. Bentley 2002 – personal communication).

A total of 12 patients were reviewed following a chondrocyte implantation combined with another surgical technique, 6 patients had a combined chondrocyte implantation and an anterior cruciate ligament (ACL) reconstruction (3 matrix induced chondrocyte implantation (MACI; Verigen, Leverkusen, Germany) and 3 autologous chondrocyte implantation (ACI)), 2 had a combined chondrocyte implantation and high tibial osteotomy (1 MACI and 1 ACI), 1 patient required bone grafting to the base of the defect followed by the chondrocyte implantation (MACI) and 3 patients had the MACI sandwich technique (Table LI).

Of the 12 patients, there were 7 men and 5 women. The mean age of the patients was 30.5 years (range 15 to 46 years) with a mean duration of symptoms of 10.46 years (range 1 year to 28 years). The mean defect size was 4.9 cm^2 (range 1.5 cm^2 to 10 cm^2) with 10 having defects in the left knee and 2 in the right. Nine patients had defects over the medial femoral condyle, 1 patient had a defect over the lateral femoral condyle, 1 over the trochlea and 1 over the medial facet of the patella (Table LII). The aetiology of the lesions included 7 (58.3%) patients who

COMBINED PROCEDURE	NUMBERS OF PATIENTS
Chondrocyte Implantation and ACL reconstruction	6
Chondrocyte Implantation and High Tibial Osteotomy	2
Chondrocyte Implantation and Bone Grafting	1
MACI Sandwich	3
Total	**12**

Table LI. Combined Chondrocyte Implantation and other surgical procedures.

ANATOMICAL DISTRIBUTION	NUMBERS OF PATIENTS
Medial femoral condyle	9
Lateral Femoral Condyle	1
Patella-single facet	1
Trochlea	1
Total	**12**

Table LII. Anatomical site of the defects found in 12 patients pre-combined ACI and other surgical procedure.

AETIOLOGY OF DEFECTS	NUMBER OF PATIENTS
Trauma	7
Osteochondritis dissecans	1
Chondromalacia Patellae	2
Previously failed cartilage resurfacing technique	2
Total	**12**

Table LIII. Aetiology of the defects found in 12 patients pre-combined ACI and other surgical procedure.

had post traumatic defects, 2 (16.6%) patients had chondromalacia patellae, 1 (8.3%) had osteochondritis dissecans and 2 (16.6%) patients who had previous cartilage resurfacing techniques which had failed (Table LIII).

The indication for surgery in all cases was pain associated with a chondral or osteochondral defect. Other symptoms included swelling, giving way, catching and locking.

Surgical Technique

The surgical technique for the ACI-C and the MACI procedure has already been described (ACI-C page 140-141 and MACI pages 203-206).

Six patients required reconstruction of the anterior cruciate ligament (ACL) (figure XXX), which was performed before implantation during the same operative procedure. In all cases a hamstring repair was used which was routed through standard tibial and femoral tunnels. Femoral fixation was achieved through a separate lateral incision with the anchoring sutures attached over a biodegradable post. The tibial fixation was secured using a biodegradable screw.

Two patients had a varus malalignment, which was corrected with a lateral closing wedge high tibial osteotomy, which was also performed before implantation under the same general anaesthetic.

Four patients had defects that were greater than 1 cm deep and it was felt necessary to use cancellous bone graft to restore congruity to the bony articular surface. One patient underwent simple bone grafting to the base of the defect and three required a MACI sandwich technique [169] based on Peterson's description [165]. In this technique after the defect had been debrided, bone graft was taken from the distal femur immediately superior to the medial femoral condyle and

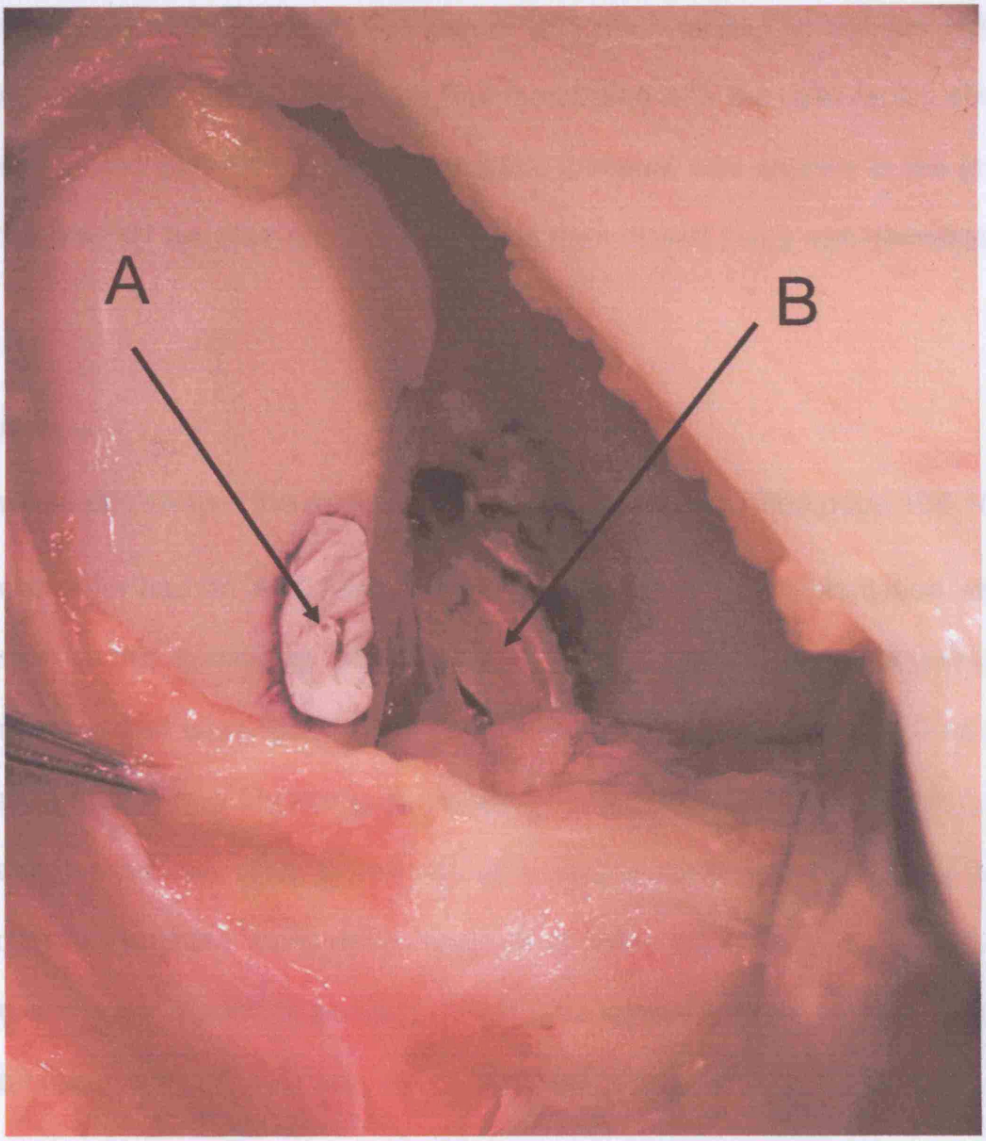

Figure XXX. Photograph of a repair of chondral defect over the medial femoral condyle with the autologous chondrocyte transplantation technique (A) and also showing a repair of the anterior cruciate ligament (B) performed at the same operation. (Courtesy of J. Skinner).

impacted into the base of the defect. Sufficient bone graft was used to restore the bony contour. Then two MACI membranes were cut to the size of the defect. The first membrane was implanted into the base of the defect with the cells facing up and was secured to the base of the defect with fibrin glue. The second MACI membrane was implanted on top of the first membrane with the cells facing down and again secured with Fibrin glue. Light digital pressure was applied to the graft for 3 minutes whilst the glue set. The knee was then closed using non-absorbable sutures.

Rehabilitation

The rehabilitation followed the same course as previously described page 108-109.

The patients who had an ACL repair as well as a chondrocyte implantation were rehabilitated in the immediate post operative period on a continuous passive motion machine and were discharged once they achieved 90° of flexion. Further rehabilitation focused on improving the patients' range of movement and muscle strengthening exercises. The 2 patients who had a combined osteotomy and chondrocyte implantation were rehabilitated in a knee brace that was locked in extension and were allowed to partially weight bear for the first two weeks. At this stage the brace was unlocked and the patients were allowed to continue partially weight bearing for a further 4 weeks. At 6 weeks after surgery the brace was removed and the patients were allowed to gradually increase the weight put through the leg as comfort allowed. Further rehabilitation focused on improving the patients' range of movement and muscle strengthening exercises.

The four patients who had either bone grafting to the base of the defect or had a MACI sandwich were rehabilitated in exactly the same way as for the standard ACI or MACI technique.

Evaluation

Patients were reviewed in the Orthopaedic Clinic at regular intervals up to 1 year. One Observer, who did not perform any of the implantations, independently reviewed the patients. Patients were evaluated clinically and arthroscopically as described on pages 109-111.

Statistical analysis. Statistical comparison of the clinical assessment scores at 1 year was by the paired Students T test. Comparisons between the good and excellent group and fair and poor group were made using the unpaired Student T test. A p value of less than 0.05 was considered statistically significant.

Results

Clinical Review

The pre-operative modified Cincinnati rating system scores are shown in table LIV, 4 (33.3%) had a good score, 7 (58.3) had a fair score and 1 (8.3%) had a poor score. As before, those 4 patients with a good score were nevertheless considered suitable for surgical intervention because they complained of considerable pain that was attributed to the articular cartilage defects. All these patients were athletic and functioned at a high level so that despite scoring badly for pain they were able to compensate on the remaining parameters of the modified Cincinnati score which in this situation tends to give a misleading impression of their symptomatology.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
12		4	7	1

Table LIV. Modified Cincinnati scores before combined ACI and other surgical procedure.

TOTAL	EXCELLENT	GOOD	FAIR	POOR
12	3	7	2	

Table LV. Modified Cincinnati scores at 1 year following combined ACI and other surgical technique.

There was a significant improvement in the modified Cincinnati score at 1 year ($p<0.005$) following surgery. Of the 12 patients who were treated by combination surgery 10 (83.3%) patients had a good or excellent result (table LV).

Table LVI shows that at 1 year of the 6 patients who had combined chondrocyte implantation and ACL reconstruction 5 (83.3%) had a good or excellent result. Of the 4 patients who had defects that required bone grafting or a MACI sandwich technique, 3 (75%) reported good or excellent results. Two patients had combined chondrocyte implantation and high tibial osteotomy and both reported good results. There was a statistically significant improvement in the modified Cincinnati scores at 1 year in the group of patients who had a combined chondrocyte implantation and anterior cruciate ligament reconstruction ($p<0.05$), however, the results for the other patient groups were not analysed because of the small numbers involved.

	TOTAL	EXCELLENT	GOOD	FAIR	POOR
Chondrocyte implantation and ACL reconstruction	6	1	4	1	
Chondrocyte implantation and high tibial osteotomy	2		2		
Chondrocyte implantation and bone graft	1			1	
MACI sandwich	3	1	2		

Table LVI. Clinical results at 1 year for 12 patients who had a combination of chondrocyte implantation with another surgical technique for chondral or osteochondral defects of the knee.

ICRS GRADE	NUMBER (%)
1, Excellent	2
2, Good	2
3, Fair	2
4, Poor	
Total	6

Table LVII. Arthroscopic results at 1 year for 6 patients, following combined ACI and other surgical procedure.

Arthroscopic review

Of the 6 patients who had a repeat arthroscopy at 1 year post implantation, 1 patient had a combined MACI and ACL repair, 2 had a combined ACI and ACL repair, 1 had an ACI and high tibial osteotomy, 1 had a MACI sandwich and 1 had a MACI and bone graft to the base of the defect.

The results of the arthroscopies at 1 year following implantation revealed ICRS grades of 1 or 2 in 4 out of 6 patients (66.6%). None of the grafts had failed at 1 year, with 2 grafts scoring 3 out of 4 on the ICRS grading system (table LVII).

The 3 biopsies taken at the time of the check arthroscopy were all from grafts located on the medial femoral condyle (1 combined MACI and ACL repair, 1 combined ACI and ACL repair and 1 combined MACI and bone graft). Hyaline cartilage was found in 1 patient based on the findings of well spaced out chondrocytes in lacunae enveloped within a matrix that stained positively for type II collagen using Safranin O. The biopsies of the two other patients showed a mixture of hyaline and fibrocartilage.

Complications

The majority of patients completed the rehabilitation programme without any complications. One patient was slow to mobilize and required a manipulation under anaesthetic. One patient complained of catching and at the check arthroscopy and was found to have graft hypertrophy that required shaving. None of the grafts failed in this review.

Discussion

Patients who have a tibiofemoral malalignment, ligamentous instability or a large bony defect require correction of these underlying abnormalities before or at the time of cartilage repair [122]. Peterson et al [72] reported on 11 patients who had a repair of the anterior cruciate ligament and a chondrocyte implantation to osteochondral defects over the femoral condyles with a mean defect size of 4.0 cm^2. At 2 years after surgery, 91% of patients reported good or excellent results. There were 2 treatment failures due to the chondrocyte implantation and 1 patient required a further operation since the ligament repair re-ruptured. Minas [167] reported on 9 patients who required a high tibial osteotomy together with an autologous chondrocyte implantation. The osteotomies were performed either before or at the same time as the cartilage repair surgery. In his study the indications for a high tibial osteotomy included defects on the weight bearing femoral condyle greater than 8-10 mm^2 or a mechanical axis deviation greater than 25% of the width of the tibial plateau and kissing lesions of the tibial and femoral condyles were also considered for this procedure. Minas observed that patients who had an ACI alone did better than those who also required a high tibial osteotomy [167].

The results of this study are encouraging with 83.3% of patients reporting a good or excellent result at 1 year although the numbers are small. Of the 6 patients who had a combination of chondrocyte implantation and anterior cruciate ligament reconstruction 83.3% reported good or excellent results and of the 2 patients who had a chondrocyte implantation and high tibial osteotomy both reported good results and are comparable with previous results published for combination techniques [72;167].

One patient had a simple cancellous bone graft to a defect that was greater than 8mm deep. At 1 year the patient reported a fair result, although this was an improvement on their pre operative score. Three patients had the MACI sandwich technique. One patient reported an excellent result and the other 2 patients reported good results at 1 year. Two of these patients formed part of a slightly larger group of 5 patients that all had the MACI sandwich technique and were recently reported in the literature [169], out of a total of 5 patients who were reviewed at 1 year, 3 had an excellent result, 1 a good and 1 a fair result.

The MACI technique is more suitable for repairing osteochondral defects of the knee in combination with other techniques since it is technically less demanding than the ACI procedure. The ACI technique is more time consuming and if performed in combination with an anterior cruciate ligament repair for example, can result in very long tourniquet and anaesthetic times. For this reason the MACI technique maybe more suitable in the repair of osteochondral defects in patients who require other surgical procedures to restore normal anatomy.

Although the importance of correcting instability and malalignment can be appreciated, it is difficult to assess whether a patients' improvement following a combined procedure is due to the chondrocyte implantation or adjunct procedure or a combination of both. A prospectively randomized study may clarify this point.

In summary, chondrocyte implantation is unlikely to succeed if normal anatomy of the knee joint is not restored prior to or at the time of chondrocyte implantation [122]. This preliminary study demonstrates that additional procedures can successfully be performed at the time of the chondrocyte implantation to restore ligament instability, malalignment and the surface bony contours of the knee joint.

CHAPTER 9:

OVERALL DISCUSSION AND CRITIQUE

Articular cartilage has many unique properties attributed to the lack of blood supply and nerve supply and the interplay between chondrocytes and the extracellular matrix they produce. These unique characteristics and its poor capacity to repair have posed a significant clinical problem in management of damaged cartilage.

Articular cartilage is susceptible to various pathologies including trauma, osteochondritis dissecans and chondromalacia patellae. Following injury there is negligable inflammation since there are no blood vessels. Very few chondrocytes undergo necrosis since having no blood supply, chondrocytes are relatively insensitive to hypoxia. Since there are no blood vessels to conduct reparative cells to the site of injury, the only possibility for repair in superficial lesions is for chondrocytes near the edges of the defect to undergo proliferation and synthesis of extracellular matrix. By contrast, injuries to articular cartilage which involve the subchondral bone precipitate the formation of a haematoma which organizes into a fibrin clot. With the ingrowth of capillaries from the subchondral bone the clot becomes granulation tissue which gradually undergoes transition to fibrocartilage containing type I and type III collagen. Although short-term this repair is quite satisfactory it does not appear to have the durability of hyaline cartilage and eventually degenerates. This is considered to be due to the preponderance of type I and type III collagen and the relative absence of type II (seen in abundance in hyaline cartilage). To a certain degree this is conjecture since relatively little is known about the natural history of osteochondral defects. Messner and Maletius [65] demonstrated both clinical and radiographic deterioration following cartilage injury

over a 14 year period in young athletes and Curl et al [15] concluded from a review of over 30,000 arthroscopies that significantly injured articular cartilage is never spontaneously restored to normal. The majority of studies describe the deterioration of early osteoarthritis to severe osteoarthritis rather than the progression of osteochondral defects to osteoarthritis.

Based on the current literature, cartilage repair techniques should be reserved for patients with symptomatic chondral or osteochondral defects rather than for preventing progression of osteoarthritis [89;91;142;167].

The presence of an articular cartilage defect is made based on the history and examination findings and confirmed with either plain radiographs for large defects or an MRI scan. The exact size and character of the defect can sometimes only be identified at arthroscopy.

Much has been written on the treatment of osteochondral defects. In the case of juvenile osteochondritis dissecans the non-operative option is best employed [52]. Patients with superficial injuries are also best untreated since long-term follow-up studies have not demonstrated progression to degenerative disease [87;88]. However, patients with symptomatic full-thickness defects should be considered for a cartilage repair technique. There are a number of surgical options available to treat these defects with varying degrees of success. Simple techniques such as lavage and debridement [24;92] of damaged cartilage, techniques that penetrate the subchondral bone to encourage a fibrocartilage repair [17;20;25;31;53;95;98;100;101], osteotomies [110-112], periosteal [123;124] or perichondral [125] grafting, autologous osteochondral grafting (mosaicplasty) [89;140-144], osteochondral allografts [35;137;138] and autologous chondrocyte implantation have been used. Scaffolds such as the matrix support prosthesis [103-105] have been used to try and improve the durability of

the fibrocartilage repair but although initial results were encouraging there remain concerns about the long-term viability of such a technique.

The most widely-used techniques at present are those that penetrate the subchondral bone resulting in a fibrocartilage repair and more recently those that result in a hyaline or hyaline-like repair such as autologous chondrocyte implantation.

There are a number of techniques involving subchondral bone penetration. Subchondral bone drilling was first described by Pridie [95] and is still the first line of treatment in many orthopaedic centres. Microfracture has been popularized by Steadman et al who reported that 75% of patients derived pain relief at 3-5 years post procedure [31].

Of the techniques that encourage a hyaline-like repair the perichondral and periosteal grafting appeared promising particularly in the animal model [123;124] however this never lived up to expectations in patients [127;128].

Osteochondral allografts may have a role in the management of young patients with large unipolar defects but there are considerable problems in accessing suitable donor tissue particularly in the U.K. because of concerns regarding the risks of transmission of infection and also the long-term viability of the donor chondrocytes.

Some success has been achieved with autogenous osteochondral grafting or mosaicplasty. Horas [142] reported encouraging results at 2 years and Hangody at 3 years [143]. In a more recent paper Hangody reported on a group of patients with a 10 year follow up, 92% of patients reported good/excellent results for femoral condyle defects [144] but the assessment parameters are not described. However, there remain concerns of donor site morbidity and patellar defects did not do as well. Hangody mentioned that the ideal defect size should be between 1-4 cm^2,

although did n't mention the mean defect size for his patients. Also no other studies have replicated his results. This indicates that mosaicplasty does not have a role in the management of defects of 4cm² or larger. Bentley et al concluded that Mosaicplasty may only have a role in the treatment of smaller defects of 1cm² or less [89].

The origins of autologous chondrocyte implantation can be traced back to Bentley and Greer's report in 'Nature' of successful transplantation in rabbits [147] and Smith's work on isolating adult articular chondrocytes in a suspension (Nature 1965). But it was Brittberg et al in 1994 [36] who first reported this technique in the treatment of osteochondral defects in human subjects. In this study they used periosteum to retain the suspension within the defect and achieved some excellent results with 14 out of 16 patients having good/excellent results.

AUTOLOGOUS CHONDROCYTE IMPLANTATION WITH A PERIOSTEAL COVER (ACI-P)

We performed a 4 year review of all patients treated with ACI-P technique. At 1 year, of the 33 patients reviewed 26 (78.8%) had good or excellent results, at 2 years 65.6% (21 out of 32 patients) and 64.7% (11 out of 17) at 3 years. At 4 years 7 patients were reviewed, 6 of whom had good or excellent results. In terms of factors that appeared to affect outcome, age and defect size had an impact. Patients in the fair or poor group at 3 years were older, had larger defects, and were much less athletic. This also seemed to be the case at other yearly reviews but did not achieve statistical significance. Defects repaired in our study were larger than those reported in other studies. Peterson et al's long term durability study reported a mean defect size of 3.4 cm² [72] compared with 5.02 cm² in our study. Also Peterson's patients had shorter duration of symptoms (3.4 years

compared with a mean of 7.3 years in our study) and fewer previous procedures. These differences may explain the disparity in terms of clinical outcome between Peterson's and our results. In our study 65.6% achieved good or excellent results at 2 years compared with 89% for the Swedish group.

The aetiology of the defect also played a role with 84.6% of patients with traumatic defects achieving good or excellent results compared with 66.6% for those with chondromalacia. However, this may have more to do with the location of the defect since patients with chondromalacia have defects over the patella and the majority of patients with traumatic defects were located over the medial femoral condyle.

At the 1 year check arthroscopy 80% of the repairs achieved ICRS grades of 1 or 2 and over 4 years just 2 grafts failed, both were located over the retropatellar surface. Encouragingly 6 out of the 13 biopsies at 1 year showed either hyaline or mixed hyaline and fibrocartilage as did all 3 biopsies at 2 years.

However, of the complications there was a high incidence of graft hypertrophy requiring arthroscopic debridement in 33% of patients at 1 year.

AUTOLOGOUS CHONDROCYTE IMPLANTATION WITH A TYPE I/III COLLAGEN COVER (ACI-C)

Using a porcine derived type I/III collagen membrane instead of a periosteum cover to retain the chondrocytes within the defect, obviates the need to extend the arthrotomy to harvest the periosteum with its associated morbidity. Of the 130 patients reviewed at 1 year 62% achieved good or excellent results, with 59% at 2 years, 59% at 3 years and 56% at 4 years. However it became clear during our study that the results in years 1, 2 and 3 were adversely affected by a group of patients who had a implantation following a previous cartilage resurfacing technique such as mosaicplasty or the matrix support prosthesis. Excluding this

group at 1 year, 68% of patients achieved good or excellent results, 64% at 2 years and 61% at 3 years. Even excluding the patients who had previous extensive cartilage repairs , there appears to be a clinical deterioration following transplantation from years 1 to 4, but this was not statistically significant (p=0.70).

As with the ACI-P group we also analysed possible factors that may affect the outcome following the ACI-C technique. Of the patients reviewed at 1 year, those that were in the good or excellent group were younger and had fewer surgical procedures. At years 2 and 3, patients in the fair and poor group had more surgical procedures before implantation than the good or excellent group. At 4 years, the patients in the fair or poor group had defects that were significantly bigger than those patients in the good or excellent group.

Of those patients arthroscoped, 84% had good/excellent repairs based on the ICRS grading system at year 1 and year 2. The majority of graft failures occurred in the first year and were to repairs over the retropatellar surface. However, this was not typical of the patellar group, with 64% of patients at 1 year reporting good/excellent results. As would be expected, patients with single defects over one facet (74% good/excellent) did better than those with repairs to both facets (42%).

As with the ACI-P group, defects repaired in this study were bigger than those reported in other studies [72;167] and also our patients had a longer duration of symptoms. As suggested previously these 2 parameters are probably related. At the Royal National Orthopaedic Hospital delays occurred in patients with symptomatic defects receiving surgical intervention due to the way patients are referred and also insufficient operating time resulting in long periods on the waiting list. This may explain the longer duration of symptoms and may also be responsible for the larger mean defect size seen at the time of implantation since the defects have had time to get bigger.

Traumatic defects again did better than defects caused by chondromalacia. But those with previous extensive cartilage repairs did worse with 24% reporting good/excellent results at 1 year, 11% at 2 years and 33% at 3 years. These defects were bigger (mean of 6.64 cm^2) and were often quite deep and the patients had a longer duration of symptoms and more operations preceding their transplantation (mean 3.29).

The histology was encouraging with 50% of biopsies showing hyaline-like or mixed hyaline and fibrocartilage repairs at 1 year and 62% at 2 years for the ACI-C group. Also in this review, patients with a hyaline-like or mixed repair reported a better clinical result although this was not statistically significant.

From this review of ACI-C it was apparent that this technique could result in a durable repair in the short to medium term.

ACI-C vs ACI-P

There has been considerable speculation as to whether the periosteum in the ACI-P technique acts simply as a watertight seal or whether it secretes growth factors necessary for the development of a hyaline-like repair. The results following our 4-year review of both techniques were similar with 68% of patients following the ACI-C technique having good or excellent results at 1 year, 64% at 2 years, 61% at 3 years and 56% at 4 years. This compared favorably with the ACI-P group with 78.8% of patients having good/excellent results at 1 year, 65.6% at 2 years, 64.7% at 3 years and 85% at 4 years (but only 7 patients were reviewed at 4 years). To be able to conclude that these 2 techniques are comparable, a prospective randomized study was carried out. There were 33 patients in the ACI-P arm and 35 patients in the ACI-C arm. At 2 years 74% of the ACI-C patients had

good/excellent results compared to 67% of the ACI-P patients. This apparent difference was not statistically significant ($p>0.05$). Arthroscopic examination also showed very similar results for both groups. Following the ACI-P technique 81% had good/excellent results and 79% following the ACI-C technique at 1 year. The biopsies reviewed at 1 year were also encouraging with 69% of the ACI-C biopsies having hyaline-like or mixed hyaline and fibrocartilage repairs and 43% following the ACI-P group. Although this looks better for the ACI-C technique the numbers involved were small.

What was also interesting in this study was the marked difference in terms of graft hypertrophy following both techniques. Previously the problems of graft hypertrophy following the ACI-P technique had been alluded to [89], but never compared directly with ACI-C in a randomized study. Within the first year following the ACI-P technique 36% of patients required shaving of a hypertrophied graft compared to one in the ACI-C group. This complication was important since patients would complain of pain and catching which was subsequently relieved by arthroscopic shaving. Graft hypertrophy following the ACI-P technique has been reported in other studies. Peterson et al reported that as many as 26 (40%) patients out of 65 had graft hypertrophy but only 7 (11%) were symptomatic [91]. In Minas' study there was a 20% incidence of graft hypertrophy and in all these cases, the patients were symptomatic. More recently in Knutsen's study there were 25% of patients following the ACI-P technique who had graft hypertrophy and required arthroscopic debridement or shaving [173].

However, the findings of this study conflicts with the animal work by Lindahl et al [157]. In his study, rabbits with artificially-created osteochondral defects had either a chondrocyte suspension injected under dead periosteum or under fresh 'live' periosteum. Of those rabbits that had the dead periosteum cover, only 1 developed

a hyaline-like repair. From these results Lindahl concluded that 'live' periosteum was needed for a successful chondrocyte implantation. However, these findings have not been supported by work in human subjects and so perhaps are an idiosyncrasy of the rabbit model. Since the ACI-C technique is comparable to the ACI-P technique both clinically and arthroscopically but results in less hypertrophy, it could be concluded that this technique is the new 'gold standard' which other techniques are compared.

There are very few randomized studies to date in the field of chondrocyte implantation. Bentley et al published a study which compared ACI with mosaicplasty [89]. This study reported that 88% of the ACI patients had good or excellent results at 1 year compared with 69% following mosaicplasty and went on to conclude that ACI was valuable for selected patients since it was able to result in a hyaline-like repair which could reduce symptoms of pain and disability.

Horas et al performed a prospective clinical study comparing ACI with osteochondral cylinder transplantation at 2 years in 40 patients with a single focal articular lesion of the femoral condyle [142]. In this study both techniques resulted in an improvement in symptoms but the ACI group seemed to lag behind the improvement provided by the osteochondral cylinder transplantation. The results were also disappointing histologically with the ACI technique since primarily the defects were filled with fibrocartilage, whereas the osteochondral cylinder transplants retained their hyaline character albeit with a persistent gap between the plugs and lack of integration with the surrounding articular cartilage. Possibly the ACI technique would be expected to lag the osteochondral cylinder transplantation technique since the ACI technique takes longer to generate repair tissue compared to the osteochondral cylinder transplantation technique which involves transplantation of differentiated hyaline cartilage into the defect from day 1. The

advantage of the ACI technique is that it can result in a hyaline-like repair which is integrated into the surrounding articular cartilage. With osteochondral cylinder transplantation there is a concern of donor site morbidity although this was not encountered in Horas' study. Horas' study only reported on 40 patients in total and their randomization involved a technique of alternating consecutive selection. Bentley et al [89] reviewed a total of 100 patients and used random sample numbers in sealed envelopes and concluded that mosaicplasty may only be useful in the treatment of small defects.

More recently a prospectively randomized study by Knutsen et al [173] compared microfracture and periosteum-covered ACI. A total of 80 patients were randomized, 40 to the microfracture technique and 40 to the ACI technique. The defects operated on were restricted to single defects over the medial femoral condyle or lateral femoral condyle. There was no clinical difference in terms of the Lysholm score at 12 and 24 months but microfracture achieved significantly better scores for the physical component of the SF36 scores at 2 years. However, as the authors suggested, this may be due to the fact that the microfracture technique is less invasive and therefore the rehabilitation is easier to complete. Although the authors reported that there was no difference between the histological appearance between the 2 repairs, they went on to say that there was a tendency for the ACI procedure to result in more hyaline cartilage repairs but it was not a significant finding with the numbers available. This suggests that their sample size was too small and possibly a difference would have been more apparent with a larger sample size. Similar clinical results were observed for both groups by Knutsen et al when they presented an update to this study at 5 years. Of note, each group sustained 9 failures (22%) at 5 years, compared with 2 failures in the ACI group

and 1 failure in the microfracture group at 2 years [174]. This was nonetheless an important study and highlighted a number of valid points regarding patient selection and the need for a simple operative technique in the treatment of osteochondral defects. One of the arguments for chondrocyte implantation is that it is one of the few techniques that can result in a hyaline-like repair with the expectation that it will last in the long-term.

MATRIX CARRIED AUTOLOGOUS CHONDROCYTE IMPLANTATION (MACI)

Following the success of the ACI-C technique a third technique has evolved of implanting cultured chondrocytes into osteochondral defects. Instead of injecting a chondrocyte suspension underneath a type I/III membrane, the chondrocytes are seeded onto one surface in the laboratory and then the membrane is cut to size and secured to the base of the defect with the cells facing downwards.

This is a relatively new technique and there are no long-term results and very few published short-term follow-up studies. Of the 107 patents reviewed at 1 year 69% had good/excellent results, this compared with 78% of the ACI-P patients and 68% for the ACI-C patients. The check arthroscopy at 1 year following the MACI technique was also encouraging with 80% of those arthroscoped having good/excellent repairs which compared favorably with the ACI-C and ACI-P results. There were 4 cases of graft failure where the graft delaminated and in 3 of those cases the defects were located over the retropatellar surface. However, like the ACI-C group this was not typical of the patellar group with 69% of patients reporting good/excellent results. This was particularly encouraging since the retropatellar surface can be very difficult to repair with the ACI-C or ACI-P technique due to the high pressures developed in the joint and the irregularity of the surface. This is particularly so when the defects are not contained (i.e. no

surrounding cartilage to suture the collagen or periosteum cover). What was interesting was that the defects over the medial femoral condyle did not seem to do as well at the 1 year mark as compared with the ACI-C or ACI-P technique. The histology was also less good, with 37.5% of biopsies having hyaline-like or mixed hyaline and fibrocartilage at 1 year. These results appear to corroborate the recent study by Behrens et al [175]. In this study 8 out of 11 patients (73%) subjectively reported that their knee was 'much better' or 'better' at 5 years which the authors observed was less than that reported for other ACI techniques, with patient satisfaction of up to 95% after 2 years [176].

Possibly these results are due to the fact that the MACI grafts take longer to mature in comparison to the ACI-C and ACI-P techniques. Zheng et al have shown in their studies [160] with the MACI membrane that chondrocytes are able to migrate from the membrane into the glue within 2 weeks. Nonetheless this fibrin glue layer through which the chondrocytes have to migrate to bond to the subchondral bone could result in a delay in the maturation of the graft. An alternative explanation is that the number of cells in the implant is approximately double with ACI compared with MACI.

From a practical viewpoint the MACI technique has clear advantages over the ACI-C and ACI-P techniques. It avoids the need to suture the membrane to the rim of the defect, it ensures a more equal distribution of chondrocytes over the defect and avoids leakage of chondrocytes, and it is also technically easier and quicker to do resulting in a shorter tourniquet time. The lesser number of cells implanted could prove to be an important defect in this method.

Therefore, despite these attractions, longer follow-up should be obtained together with prospectively randomized studies before widespread usage of this technique.

OTHER POTENTIAL SCAFFOLDS FOR AUTOLOGOUS CHONDROCYTE IMPLANTATION

As mentioned earlier there are some limitations associated with the periosteum-covered ACI, including the complexity and morbidity associated with the surgical procedure and the frequent occurrence of periosteal hypertrophy[177]. In the conquest to reduce the complexity of this technique and also to reduce the size of incision needed to carry out the transplantation, alternative methods of implanting the chondrocytes have been suggested. The MACI technique involves a type I/III collagen scaffold, to which the chondrocytes attach themselves and are able to redifferentiate and produce an extracellular matrix, however there are other scaffolds which have been suggested. The most popular alternatives in the literature include an agarose or alginate gel [178-181] and a hyaluronan matrix [182;183].

In the past agarose gels have been used due to their capacity to stabilize the chondrocyte phenotype [149;184] and although calcium alginate gels represent a carrier material with similar biological properties, they have other advantages [180;185]. Gels such as agarose [149;184] and alginate [179;186-188] are able to maintain the spherical shape of chondrocytes and also enable them to divide and express proteins characteristic of articular cartilage. However, within alginate gels, the average half-life of proteoglycans synthesized by chondrocytes is twice as long than if they were cultured in agarose gels [186], which is similar to the turnover in normal articular cartilage [185]. Also, observations made following immunohistochemical analyses suggest that matrix formed in alginate gels was compartmentalized corresponding to the pericellular and territorial matrix which

does not occur with agarose gels [189]. Alginate gels also have the advantage that they are readily biodegradable [180]. The calcium ions bound to the alginate are slowly replaced with ions that are not gel-inducing such as sodium ions resulting in softening of the gel and its eventual breakdown. Also, substances such as phosphate or citrate having a strong affinity for calcium ions will rapidly break up the calcium alginate complex and dissolve the gel.

In this technique the chondrocytes are cultured in the monolayer technique as described for the MACI technique and then the chondrocytes are suspended in a low viscosity alginate solution [186]. This solution can be pipetted into silicone moulds which have been placed on a pad soaked in calcium chloride. As soon as the gel/chondrocyte suspension comes into contact with the calcium chloride, 'gelation' of the alginate occurs. Following the animal studies of Hedbom et al [180], they demonstrated that cultured chondrocytes in an alginate construct had the same cellularity as normal cartilage, with 20-25% of the normal proteoglycan concentration and 40-50% of the normal collagen concentration and could be cultured in vitro for 120 days. They concluded that the capacity of alginates to preserve the chondrocyte phenotype and the relatively high anabolic rate of the cells that they observed from their animal studies could lead to the adoption of this technique in vivo.

However, subsequent studies have been more circumspect. Mierisch et al [181], reported on the fate of genetically-marked chondrocytes following their implantation within a calcium alginate scaffold. They confirmed findings from other studies that chondrocytes were able to maintain their spherical shape within an alginate gel [179;186-188] and also noted the upregulation of cartilage-specific genes for aggrecan and type II collagen. However, they noted that in vivo cells were detectable for only 4 weeks, and their number seemed to diminish with time. They

suggested that although nutrients could diffuse through the alginate gel, chondrocytes were not able to migrate out of the gel. Also, with time the gel loses its structural integrity and as a result the implanted cells lose their structural support. They concluded from their observations that implanted chondrocytes are neither incorporated into the host tissue nor do they contribute to the repair of the osteochondral defect and any repair that does occur is due to the surrounding host cells. However, these results were obtained from an animal model and they used chondrocytes derived from rib cartilage rather than articular chondrocytes.

Grunder et al [178], concluded from their study of 11 patients with an average age of 39.8 years that articular chondrocytes cultured in alginate beads showed upregulation of type II collagen and downregulation of type I collagen. Also the addition of BMP-2 seemed to have a positive effect on this up-regulation, with increased expression of collagen type II and aggrecan expression. However, consistent with other authors [190], the growth of cells in alginate alone may not be sufficient for cell expansion due to their low proliferation rates and are unlikely to be sufficient for cartilage implantation techniques.

Hyaluronic acid (Hyaluronan) is a glycosaminoglycan that is widely distributed in the body. HYAFF® 11 (Fidia Advanced Biopolymers, Abano, Terme, Italy) is an esterified derivative of hyaluronan, which can be used to produce a number of biodegradeable structures with different shapes. Hyalograft® C (Fidia Advanced Biopolymers, Abano, Terme, Italy) is a tissue engineered graft composed of autologous chondrocytes grown on a HYAFF® 11 scaffold. The technique of implanting Hyalograft® C into full thickness osteochondral defects has been used in a number of European countries since 1999, with more than 3600 patients treated [182]. The advantage of this technique over the periosteum-covered ACI technique is that it involves a much smaller surgical incision and often does not

require any sutures or fibrin glue to secure it to the rim of the defect because of the intrinsic adhesive properties of the hyaluronan scaffold [191]. Marcacci et al [182] reported on 141 patients with follow-up ranging form 2 to 5 years and a mean age of 37.6 years. After a mean follow-up of 38 months after implantation, 91.5% of patients were subjectively improved. There was a 5% failure rate, although the authors observed that these failures occurred in patients who would have otherwise had an arthroplasty but had the Hyalograft® C technique in an attempt to delay it.

Nehrer et al [183] reviewed 36 patients with a mean age of 33 years. At 3 years they reported 87% good or excellent results and no failures.

These are encouraging preliminary results, however longer follow-up and randomised controlled trials comparing Hyalograft® C with ACI would be useful to demonstrate whether this technique is a valid alternative.

CHONDROCYTE IMPLANTATION AND COMBINED PROCEDURES

It has been well documented that prior to cartilage repair any instability or malalignment of the joint should be corrected [122]. Any laxity of the anterior cruciate ligament after chondrocyte implantation could result in abnormal translation and rotation of the femur on the tibia resulting shearing of the graft and failure of the repair. Similarly, if limb malalignment is not corrected then excessive loading on the graft could lead to its failure. Previous authors [153] have suggested that patients with large osteochondral defects who have normal alignment may benefit from an unloading osteotomy. In this study the practice was to perform osteotomies only in patients with a significant varus or valgus malalignment.

Brittberg also suggested that he found that defects with depths greater than 8mm benefited from bone grafting to restore the bony contour [153] this was also the practice in this study.

A total of 12 patients were reviewed following chondrocyte implantation combined with another surgical technique. The results were encouraging, with 83% of the combined chondrocyte transplantations and ACL reconstructions having good or excellent results at 1 year. Both patients who had a combined chondrocyte implantation and osteotomy had similar results as well as those patients that had the MACI sandwich technique. One patient had a simple bone graft to their lesion before a graft was then implanted and reported only a fair result at 1 year, albeit an improvement from their pre-operative score.

This study highlighted a number of important issues. Firstly it supports conclusions drawn from other studies [122;153] that instability and malalignment must be corrected prior to or at the time of chondrocyte implantation to avoid excessive loading on the repair. It also showed that successful results could be achieved following combined techniques but the difficulty is in determining whether the success is due to one or either of the techniques or a combination of both. For this question to be addressed a randomized controlled trial would be needed to address this issue. What was evident from this study was that although it was possible to perform an ACL reconstruction and MACI technique as a one-stage procedure, there was considerable difficulty in performing an ACL reconstruction and ACI repair due to time constraints imposed by the tourniquet.

Critique

With a study of this size there were a number of difficulties which had to be overcome. Some patients were unable to attend clinic and so that a proportion of the clinical and functional scores were made either by telephone or by way of a postal questionnaire. Since the Royal National Orthopaedic Hospital is a tertiary referral hospital with patients all over the country this was unavoidable. However, all the assessment was performed by independent research staff who had no part in the surgical procedure.

It was intended that all patients would have a '2nd look' arthroscopy at 1 and 2 years post-operatively, however as is apparent from this thesis this was not the case. This was due to a few patients not attending their follow up arthroscopy and the technical difficulty of accessing some grafts by arthroscopic means especially in the patello-femoral joint.

In this study we used the Modified Cincinnati Rating system to asses the patients both clinically and functionally. Some authors do not use this scoring system, making a direct comparison of results difficult. Knutsen in his recent study used the Lysholm, Tegner and Meyers scores [173] and Peterson et al used the Lysholm, Cincinnati knee score, Modified Noyes Cincinnati rating, Wallgren-Tegner score and the Brittberg Clinical score [91] and Minas used the Cincinnati rating scale, Knee society score, Western Ontario McMaster Universities Osteoarthritis Index and the SF36. All these scoring systems are similar, but if different centres adopted the same scoring systems then comparisons could be made more easily. During the course of this study the SF36 questionnaire was adopted, which has the advantage of assessing the patients psychological profile as well as their physical status before and after surgery. Possibly this scoring system in conjunction with

one other functional scoring system such as the Modified Cincinnati Rating would be acceptable to other centres involved in Chondrocyte implantation.

There was some discussion as to whether the author should assess all the biopsies for this study however since the author knew which procedure each patient had there was the possibility of bias and as a result the Consultant Histopathologist agreed to assess the grafts and was blinded as to whether the patients had either a MACI, ACI-C or ACI-P.

Another question encountered in this study was how best to assess the biopsies of the grafts taken at 1 and 2 years. In discussion with the Histopathologist at The Royal National Orthopaedic Hospital we concluded that a graft with sparse, oval-shaped chondrocytes, evenly distributed in lacunae through the majority of the biopsy enveloped in extracellular matrix with a homogenous glassy appearance which stained with Safranin O, without the evidence of collagen fibrils and absence of blood vessels and nerves which had bonded to the subchondral bone was hyaline or hyaline-like cartilage. In contrast, grafts that were considered to be fibrocartilage had a high proportion of disorganised coarse type I collagen fibres with more frequent and elongated cells. The real problem was in agreeing what was mixed hyaline and fibrocartilage. In the end we used the same criteria as Knutsen [173], if more than 60% of the core biopsy was hyaline cartilage it was considered hyaline –like, if it was less than 40% than it was considered to be that of fibrocartilage. Core biopsies containing more than 40% hyaline cartilage but less than 60% were considered to be that of a mixed hyaline and fibrocartilage. This is however fairly arbitrary but at present there is not a suitable alternative that is reproducible. Similarly, Peterson et al [91] described the histological appearance based on a number of criteria including cellularity, columnar structure of the cartilage and its appearance in polarized light and they also used immunostaining

for Type II collagen. However, in Peterson et al's study the authors did not explain how they concluded that a graft had the appearance of 'mixed tissue'. Again as with the clinical scoring system, a universally-agreed classification would make comparisons between different centres a lot easier. After 5 years consideration of this matter the ICRS has yet to publish a definitive histological scoring system which indicates the difficulty of precise assessment.

The majority of patients presented in this study had a follow up of 1 or 2 years with a few patients who had been reviewed at 3 and 4 years. Although this study comprehensively presents the short to medium term results there is no data for the long term results at this centre, although this forms part of an ongoing project.

CHAPTER 10:

SUGGESTIONS FOR FURTHER RESEARCH

PROSPECTIVELY RANDOMISED STUDIES

There is a clear need for more prospectively randomised studies in this field. Knutsen's [173] study was particularly interesting in comparing periosteum covered ACI and microfracture. Knutsen proposed that in the short-term, microfracture had the slight edge on autologous chondrocyte implantation but this study may have inadequate statistical power. However, the real test is the durability of the repair in the mid to long-term. Therefore a longer study comparing collagen covered ACI with microfracture at 8 years to 10 years would help dispel any doubts about which of these techniques is the most successful.

During the course of this study it was apparent that collagen-covered ACI produced repairs with similar characteristics to periosteum-covered ACI as regards clinical outcome, arthroscopic appearance and histological assessment of the graft. However the periosteum-covered ACI resulted in considerably more morbidity in terms of graft hypertrophy which required arthroscopic shaving since it caused catching and pain. It is proposed from this study that collagen-covered ACI is the new 'gold standard' in autologous chondrocyte implantation. Therefore in any new prospectively randomised studies comparisons should be made with the collagen-covered ACI as apposed to the periosteum-covered ACI the previous 'gold standard' in chondrocyte implantation. Currently there is a multi-centre study comparing MACI with collagen covered ACI based at the Royal National Orthopaedic Hospital, Stanmore.

REHABILITATION

Almost all centres adopt a different rehabilitation program. For example patients in this study were encouraged to fully weight-bear from the start since it is thought that load-bearing is important for the maintenance of the function of the recipient cartilage and possibly for stimulating the differentiation of the implanted chondrocytes. Peterson's [91] patients were only allowed to partially weight-bear for the first 8 weeks and were then allowed to fully weight bear from 8 to 12 weeks which was the same rehabilitation program that Knutsen [173] used whereas Minas [167] prevented his patients from weight-bearing for 6 weeks and then used progressive weight-bearing to full weight-bearing at 4 months. In Australia Wood et al give their patients a course of pre-operative physiotherapy (verbal communication). All of these groups use continuous passive motion (CPM) in the early post-operative period because it is thought that this stimulates the isolated implanted cells to produce more type II collagen, based on Salter's' observations [62]. A prospectively randomised study comparing 3 or 4 of the most widely-adopted rehabilitation programs may show that one rehabilitation program is better than the others. This may encourage the universal adoption of 1 rehabilitation program, making direct comparisons between different centres easier.

FUTURE TECHNOLOGIES

A possible area for future research in this field is the adoption of stem-cell technology so that cells harvested from the peripheral blood could then be cultured to produce chondrocytes and then implanted into osteochondral defects. Roufosse et al [192] confirmed that although there is evidence for circulating mesenchymal precursor cells which are able to differentiate into a number of mesenchymal tissues including cartilage there are difficulties in obtaining conclusive and

reproducible results. They concluded that the inconsistent results were due to variations in 'methods of cell purification, culture and characterisation'. Nonetheless, this would suggest that it is a realistic aim to be able to take a blood sample and culture chondrocytes from it that are able to produce type II collagen.

From my clinical review of patients who underwent autologous chondrocyte implantation, it became apparent that in the short-term there was considerable morbidity associated with the arthrotomy which was made during the second stage of the procedure. Patients complained of pain and tightness over the scar in the immediate post-operative period. In the short-term this undoubtedly hampered the patients' ability to follow the rehabilitation program and delayed their recovery. From this observation I considered other ways to deliver the chondrocytes to the osteochondral defect.

A fascinating field of medicine which has made some impact in the field of oncology and also diagnostics amongst others is monoclonal antibody technology. In Oncology it has been used to deliver chemotherapeutic agents to tumours and perhaps this same technology could be used to deliver chondrocytes to exposed subchondral bone. The Fc component of the monoclonal antibody could bind to a surface antigen on the chondrocyte and the Fab component to surface antigens on osteoblasts or to the matrix itself. This would still be a 2-stage technique, the first requiring an arthroscopy and chondrocyte harvesting and the second stage the administering of a chondrocyte/monoclonal antibody suspension in the form of an intra-articular injection. The second stage would probably still require an arthroscopy to debride the defect and expose the subchondral bone. This technique would also ensure direct contact between the chondrocytes and the underlying bone although there would be a small gap bridged by the monoclonal antibody. Lance [193] was the first to establish specific monoclonal antibodies for

human articular chondrocytes HUMC 1-5. Buija et al [194] went on to discover that there was a cross reaction with human fibroblasts and osteoblasts for the antibodies HUMC 2 and 5. However, they concluded that HUMC 1, 3 and 4 were specific for chondrocytes and suggested that they could be used in immunohistological analysis. Possibly with this technology an Fc component could be designed that would bind to either HUMC 1, 3 or 4 and a Fab component that could bind to a specific surface marker on osteoblasts or the bone matrix. The author proposes a pilot study to first identify which specific surface antigens have been isolated for cellular structures of chondrocytes and osteoblasts and then perform an in vitro study to analyse the relationship between the antibodies, chondrocytes and osteoblasts and their matrix.

The need for a simple procedure to generate a durable repair that shares the characteristics of normal articular cartilage in the treatment of osteochondral defects will ensure that this remains an exciting field for many years to come.

CHAPTER 11:

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CHAPTER 12 APPENDIX I: DATA COLLECTION FORM

PATIENT DETAILS						
PATIENT NAME						
MALE			FEMALE			
HOSPITAL NUMBER						
DATE OF BIRTH						
AGE AT TIME 0F SURGERY (2ND STAGE)						
OCCUPATION						
SMOKER			*NO*		*YES*	
OPPOSITE KNEE	*NORMAL*		*ALMOST NORMAL*		*NOT NORMAL*	
MEDICATION	*NSAIDS*		*CORTICOSTEROIDS*		*OTHER*	
INDICATION FOR OPERATION						
DURATION OF SYMPTOMS						

PREVIOUS KNEE SURGERY	
ARTHROSCOPY	
MENISECTOMY	
ARTICULAR CARTILAGE IMPLANTATION	
MOSAICPLASTY	
DRILLING / MICROFRACTURE	
ARTHROSCOPY + REMOVAL OF LOOSE BODIES	
OTHER	

SIDE	
RIGHT	
LEFT	

AETIOLOGY OF DEFECTS	
TRAUMA	
OSTEOCHONDRITIS DISSECANS	
CHONDROMALACIA PATELLAE	
EARLY OA	
OTHER (? TRAUMA)	

EXAMINATION FINDINGS & SCORING SYSTEM AT TIME OF CARTILAGE IMPLANTATION								
WASTING	*NIL*		*<2CM*		*>2CM*			
ALIGNMENT	*NORMAL*		*VALGUS*		*VARUS*			
EFFUSION	*NIL*		*MILD*		*MOD*		*SEV*	
RANGE OF MOVEMENT (DEGREES)								
CREPITUS	*NIL*		*MILD*		*MOD*		*SEV*	
EXTENSION								
JOINT TENDERNESS	*NIL*		*LATERAL*		*MEDIAL*		*PFJ*	
EXT. LAG								
PATELLA TRACKING	*STABLE*		*UNSTABLE*		*J SIGN*			
ABILITY TO SQUAT	*NORMAL*		*DIFFICULT*		*UNABLE*			
ANTERIOR DRAW	*0*		*1*		*2*		*3*	
MCL INSTABILITY	*0*		*1*		*2*		*3*	
LCL INSTABILITY	*0*		*1*		*2*		*3*	
LACHMAN TEST	*0*		*1*		*2*		*3*	
POSTERIOR SAG	*0*		*1*		*2*		*3*	
PIVOT SHIFT	*POSITIVE*				*NEGATIVE*			
VISUAL ANALOGUE SCORE (0-10)								
BENTLEY FUNCTIONAL RATING SYSTEM (0-4)								

CINCINATTI RATING SYSTEM			
	PAIN	*(OUT OF 20)*	
	GIVING WAY	*(OUT OF 20)*	
	SWELLING	*(OUT OF 10)*	
	WALKING ABILITY	*(OUT OF 10)*	
	STAIR WALKING	*(OUT OF 10)*	
	RUNNING	*(OUT OF 5)*	
	JUMPING/TWISTING	*(OUT OF 5)*	
	OVERALL ACTIVITY	*(OUT OF 20)*	
	TOTAL	*(OUT OF 100)*	

INVESTIGATIONS BEFORE CARTILAGE IMPLANTATION					
XRAY FINDINGS	VALGUS ANGLE		SULCUS ANGLE		
	PATELLA	*BAJA*		*ALTA*	
	DEFECT VISIBLE	*YES*		*NO*	
	DEPTH (mm)				
MRI FINDINGS	DEFECT VISIBLE	*YES*		*NO*	
	DEFECT SIZE (mm)	*WIDTH*		*DEPTH*	

ANATOMICAL DISTRIBUTION OF CARTILAGE DEFECTS	
MEDIAL FEMORAL CONDYLE	
PATELLA-SINGLE FACET	
PATELLA MULTI-FACETS	
LATERAL FEMORAL CONDYLE	
TROCHLEAR	
LATERAL TIBIAL CONDYLE	

NUMBER OF LESIONS	
SINGLE	
MULTIPLE	

SIZE OF DEFECTS (mm)	
1	
2	

CONSULTANT:		COMPLETED BY:		DATE:	

HOW ARE CHONDROCYTES APPLIED	
MACI	
ACI	
OTHER (EG. COMBINED PROCEDURE)	

TYPE OF GRAFT	
PERIOSTEUM	
TYPE I/III COLLAGEN MEMBRANE	

NUMBER OF CELLS GRAFTED	

COMBINED PROCEDURES	
ACI + OSTEOTOMY	
ACI + ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION	

EXAMINATION FINDINGS & SCORING SYSTEM POST CARTILAGE IMPLANTATION								
WASTING	*NIL*		*<2CM*		*>2CM*			
ALIGNMENT	*NORMAL*		*VALGUS*		*VARUS*			
EFFUSION	*NIL*		*MILD*		*MOD*		*SEV*	
RANGE OF MOVEMENT (DEGREES)								
CREPITUS	*NIL*		*MILD*		*MOD*		*SEV*	
EXTENSION								
JOINT TENDERNESS	*NIL*		*LATERAL*		*MEDIAL*		*PFJ*	
EXT. LAG								
PATELLA TRACKING	*STABLE*		*UNSTABLE*		*J SIGN*			
ABILITY TO SQUAT	*NORMAL*		*DIFFICULT*		*UNABLE*			
ANTERIOR DRAW	*0*		*1*		*2*		*3*	
MCL INSTABILITY	*0*		*1*		*2*		*3*	
LCL INSTABILITY	*0*		*1*		*2*		*3*	
LACHMAN TEST	*0*		*1*		*2*		*3*	
POSTERIOR SAG	*0*		*1*		*2*		*3*	
PIVOT SHIFT	*POSITIVE*				*NEGATIVE*			
VISUAL ANALOGUE SCORE (0-10)								
BENTLEY FUNCTIONAL RATING SYSTEM (0-4)								

CINCINATTI RATING SYSTEM			
	PAIN	*(OUT OF 20)*	
	GIVING WAY	*(OUT OF 20)*	
	SWELLING	*(OUT OF 10)*	
	WALKING ABILITY	*(OUT OF 10)*	
	STAIR WALKING	*(OUT OF 10)*	
	RUNNING	*(OUT OF 5)*	
	JUMPING/TWISTING	*(OUT OF 5)*	
	OVERALL ACTIVITY	*(OUT OF 20)*	
	TOTAL	*(OUT OF 100)*	

INVESTIGATIONS POST CARTILAGE IMPLANTATION					
XRAY FINDINGS	VALGUS ANGLE		SULCUS ANGLE		
	PATELLA	*BAJA*		*ALTA*	
	DEFECT VISIBLE	*YES*		*NO*	
	DEPTH (mm)				
MRI FINDINGS	DEFECT VISIBLE	*YES*		*NO*	
	DEFECT SIZE (mm)	*WIDTH*		*DEPTH*	

EMPLOYMENT STATUS								
STOPPED WORK BEFORE CARTILAGE IMPLANTATION	YES		NO					
TIME OFF WORK								
RETURNED TO WORK POST CARTILAGE IMPLANTATION	*NO*		*PART TIME*		*FULL TIME*			
TIME AFTER SURGERY WHEN RETURNED TO WORK								

INTERNATIONAL CARTILAGE RESEARCH SOCIETY ARTHROSCOPIC GRADING OF GRAFT BIOSY	
ICRS 1 - EXCELLENT	
ICRS 2 - GOOD	
ICRS 3 - FAIR	
ICRS 4 - POOR	

ADDITIONAL INFORMATION								
TIME OF CHECK ARTHROSCOPY								
FIRMNESS	*EXCELLENT*		*GOOD*		*FAIR*		*POOR*	
BIOPSY RESULTS	*FIBROCARTILAGE*		*HYALINE*		*MIXED*			
FOLLOW-UP								

REHABILITATION PROGRAM	
STANDARD	
OTHER (EG. WITH COMBINED PROCEDURES)	

COMPLICATIONS	
SLOW TO MOBILISE REQUIRING MUA	
UNPLANNED ARTHROSCOPY	
THROMBO EMBOLIC PHENOMENON	
INFECTION	
GRAFT FAILURE	
GRAFT HYPERTROPHY	

APPENDIX II: **Modified Cincinnati Rating System Questionnaire**

This questionnaire has been designed to give your therapist information as to how your knee pain has affected your ability to manage in everyday life. Please answer every question by placing a mark in the one box that best describes your condition today.
We realize you may feel that 2 of the statements may describe your condition, but please mark only the box that most closely describes your current condition.

Section 1 - Pain Intensity

20 No pain, normal knee, performs 100%.

16 Occasional pain with strenuous sports or heavy work, knee not entirely normal, some limitations but minor and tolerable.

12 Occasional pain with light recreational sports or moderate work activities, running or, heavy labour, strenuous sports.

8 Pain, usually brought on by sports, light recreational activities or moderate work. Occasionally occurs with walking, standing or light work.

4 Pain is a significant problem with simple activity such as walking, relieved by rest, unable to do sports.

0 Pain present all the time. Not relieved by rest.

Section 2 - Swelling

10 No swelling

8 Occasional swelling with strenuous sports or heavy work. Some limitations but minor and tolerable.

6 Occasional swelling with light recreational sports or moderate work activities. Frequently brought on by vigorous activities, running, heavy labour, and strenuous sport.

4 Swelling limits sports and moderate work. Occurs infrequently with simple walking activities or light work (approx 3 times a year).

2 Swelling brought on by simple walking activities and light work. Relieved by rest.

0 Severe problem all the time, with simple walking activities.

Section 3 - Giving Way

20 No giving way.

16 Occasional giving way with strenuous sports or heavy work.Can participate in all sports but some guarding or limitations present.

12 Occasional giving way with light sports or moderate work. Able to compensate but limits vigorous activities, sports, or heavy work not able to cut or twist suddenly.

8 Giving way limits sports and moderate work, occurs infrequently with walking or light work (approx 3 times per year).

4 Giving way with simple walking activities and light work. Occurs once per month, requires guarding.

0 Severe problem with simple walking activities, cannot turn or twist while walking without giving way.

Section 4 - Overall activity level

20 No limitation, normal knee, able to do everything including strenuous sports or heavy labour.

16 Perform sports including vigorous activities but at lower performance level: involves guarding or some limits to heavy labour.

12 Light recreational activities possible with rare symptoms, more strenuous activities cause problems.Active but in different sports; limited to moderate work.

8 No sports or recreational activities possible. Walking with rare symptoms; limited to light work.

4 Walking, ADL cause moderate symptoms, frequent limitations.

0 Walking, ADL cause severe problems, persistent symptoms.

Section 5 - Walking.

10 Walking unlimited.

8 Slight/mild problem.

6 Moderate problem: smooth surface possible up to approx 800m.

4 Severe problem, only 2-3 blocks possible.

2 Severe problem; requires stick or crutches.

Section 6 - Stairs

10 Normal, unlimited.

8 Slight/mild problem.

6 Moderate problems only 10-15 steps possible.

4 Severe problem; requires bannister support.

2 Severe problem only 1-5 steps possible

Section 7 - Running activity

5 Normal, unlimited; fully competitive, strenuous.

4 Slight mild problem; run half speed.

3 Moderate problem 2-4 km.

2 Severe problem only 1-2 blocks possible.

1 Severe problem only a few steps.

Section 8 - Jumping or Twisting

5 Normal, unlimited, fully competitive, strenuous.

4 Slight to mild problem; some guarding but sport possible..

3 Moderate problem; gave up strenuous sports, recreational sports possible.

2 Severe problem; affects all sports; must constantly guard.

1 Severe problem; only light activity possible (golf, swimming).

TOTAL OUT OF 100:

SPECIAL NOTE

THIS ITEM IS BOUND IN SUCH A MANNER AND WHILE EVERY EFFORT HAS BEEN MADE TO REPRODUCE THE CENTRES, FORCE WOULD RESULT IN DAMAGE

APPENDIX III: TABLE OF RESULTS

Pat no.	Age (yrs)	Sex	Cause	No. of ops	Dur. Of symp (mths)	Cin Pre Op	Site	Size (mm^2)	Surg Proc	Date of 2nd stage	Cin 1 yr	Cin 2 yrs	Cin 3 yrs	Cin 4 yrs	Notes
1	34	F	Chond-P	2	24	56	L pat med	875	ACI-P	28/9/01	44	65			P vs C
2	17	F	Chond-P	1	30	46	R pat lat	96	ACI-P + lat rel	15/5/01	44	30			P vs C
3	31	M	Trauma	1	36	69	L troch	195	ACI-P	18/12/01	52				
4	24	F	Chond-P	1	60	60	R Pat	500	ACI-P	22/02/01	51	89	100		P vs C
5	34	F	Trauma	2	60	32	L MFC	600	ACI-P	28/3/00	38	42	52		P vs C
6	46	F	Chond-P	3	90	10	R pat sing	875	ACI-P	9/10/01	36	26			P vs C
7	32	F	Chond-P	2	156	32	L pat med	330	ACI-P	7/12/01	28	18			P vs C
8	36	F	Chond-P	1	12	38	L pat multi	800	ACI-P	21/9/01	66	56			P vs C
9	37	F	Trauma	2	18	18	L pat sing L troch	420 250	ACI-P + lat rel ACI-P	1/7/00	84	50	24		P vs C
10	37	M	Trauma	1	19	64	R MFC	400	ACI-P	16/11/99	75	55	42	24	P vs C
11	39	F	Chond-P	2	24	18	R pat	360	ACI-P	10/3/00	70	52	54	68	P vs C
12	28	M	Trauma	2	24	67	R LFC	375	ACI-P	24/3/00	90	90	88	89	P vs C
13	26	F	Chond-P	1	24	56	L pat multi	384	ACI-P	26/6/01	69	83			P vs C
14	39	M	Chond-P	3	24	62	R troch	450	ACI-P + div of med plica	21/9/01	76	80			P vs C
15	33	M	Trauma	1	36	34	R pat	875	ACI-P	14/5/99	71	36	50	60	P vs C
16	21	M	Chond-P	1	48	55	L pat lat	300	ACI-P	16/3/01	84	94			P vs C
17	30	F	Chond-P	1	48	73	L pat multi	300	ACI-P	2/2/01	69	52	64		P vs C
18	35	M	Trauma	3	48	28	R pat multi	525	ACI-P + mosaic to troch	16/10/01	67	83			P vs C

SPECIAL NOTE

THIS ITEM IS BOUND IN SUCH A MANNER AND WHILE EVERY EFFORT HAS BEEN MADE TO REPRODUCE THE CENTRES, FORCE WOULD RESULT IN DAMAGE

Pat no.	Age (yrs)	Sex	Cause	No. of operations	Dur. Of symp.	Cin Pre Op	Site	Size (mm^2)	Surg Proc	Date of 2nd stage	Cin 1 yr	Cin 2 yrs	Cin 3 yrs	Cin 4 yrs	Notes
19	23	M	Chond-P	4	60	21	L pat	187.5	ACI-P + mosaic to troch	12/3/99	60	68	76	86	P vs C
20	15	F	OCD	1	60	73	R MFC	700	ACI-P	9/3/01	74	86			P vs C
21	38	M	Trauma	2	72	88	L LFC	150	ACI-P + drilling	5/10/99	65	90	78	74	P vs C
22	20	F	OCD	1	72	26	L MFC	525	ACI-P	15/9/00	89	53	59		P vs C
23	33	M	Other	3	84	24	R pat sing	400	ACI-P	15/9/00	58	61	65		P vs C
24	26	F	Trauma	1	108	48	R MFC	375	ACI-P	15/9/00	87	71	70		P vs C
25	27	M	Trauma	1	120	33	R MFC	300	ACI-P	3/10/00	71				
26	22	F	Chond-P	1	120	62	L pat multi	360	ACI-P	27/4/01	86	55			P vs C
27	26	M	OCD	4	120	44	R LFC	900	ACI-P	8/2/00	84	69			P vs C
28	26	F	Chond-P	2	144	42	R pat	360	ACI-P	24/10/00	93	56	56		P vs C
29	26	M	OCD	2	156	20	R MFC	600	ACI-P	18/2/00	66	10	10		P vs C
30	32	M	Trauma	4	180	68	R MFC	600	ACI-P	25/5/99	77	76			P vs C
31	25	F	Chond-P	1	216	43	L pat	200	ACI-P + drilling harvest site	28/3/00	70	86	70	82	P vs C
32	39	F	Trauma	4	276	41	L troch	300	ACI-P + ACL recon	2/2/01	68	68	69		P vs C, comb
33	52	M	Trauma	2	324	72	R pat multi	989	ACI-P	1/2/02	82	100			P vs C
34	23	M	OCD	4	120	50	L MFC	660	ACI-P	27/04/01		71			P vs C
35	33	F	Trauma	8	216	10	R pat multi	800	ACI-P	07/12/01		18			P vs C
34	27	F	Chond-P + trauma	2	198	57	L MFC	300	ACI-C	26/04/01	77	79			

SPECIAL NOTE

THIS ITEM IS BOUND IN SUCH A MANNER AND WHILE EVERY EFFORT HAS BEEN MADE TO REPRODUCE THE CENTRES, FORCE WOULD RESULT IN DAMAGE

Pat no.	Age (yrs)	Sex	Cause	No. of operations	Dur. Of symp.	Cin Pre Op	Site	Size (mm^2)	Surg Proc	Date of 2nd stage	Cin 1 yr	Cin 2 yrs	Cin 3 yrs	Cin 4 yrs	Notes
35	17	M	Chond-P	1	60	59	L pat	800	ACI-C	18/01/00	57	73	76		P vs C
36	32	F	Chond-P	3	144	32	L pat	270	ACI-C	26/03/99	86	79	66	46	P vs C
37	27	F	Chond-P	1	180	38	L pat med	225	ACI-C	19/02/02	90				MACI vs ACI
38	39	F	Chond-P	2	120	20	L pat multi	559	ACI-C	08/03/02	20				
39	27	F	Chond-P	3	156	58	L pat multi	500	ACI-C	13/07/01	58	52			P vs C
40	42	M	Chond-P	3	216	50	L pat multi	600	ACI-C	28/05/02	66				MACI vs ACI
41	17	F	Chond-P	3	72	35	L pat sing	400	ACI-C	07/09/99	45	38	32		
42	25	F	Chond-P	1	144	50	L pat sing	595	ACI-C	22/01/02	64				MACI vs ACI
43	32	F	Chond-P	1	60	44	L pat sing	150	ACI-C	02/11/01	64				
44	19	F	Chond-P + trauma	2	78	23	R LFC	300	ACI-C	15/05/00	68	38	34		P vs C
45	34	F	Chond-P	2	120	25	R pat	300	ACI-C	24/11/00	26	36			
46	24	M	Chond-P	1	60	28	R pat	300	ACI-C	07/09/99	62	67	86		P vs C
47	22	F	Chond-P	2	144	18	R pat	500	ACI-C	19/01/99	62	40	32	36	
48	33	F	Chond-P	3	144	32	R pat	126	ACI-C	18/01/00	79	38	43		
49	31	F	Chond-P	1	120	40	R pat lat	200	ACI-C	08/02/02	18				MACI vs ACI

SPECIAL NOTE

THIS ITEM IS BOUND IN SUCH A MANNER AND WHILE EVERY EFFORT HAS BEEN MADE TO REPRODUCE THE CENTRES, FORCE WOULD RESULT IN DAMAGE

Pat no.	Age (yrs)	Sex	Cause	No. of operations	Dur. Of symp.	Cin Pre Op	Site	Size (mm^2)	Surg Proc	Date of 2nd stage	Cin 1 yr	Cin 2 yrs	Cin 3 yrs	Cin 4 yrs	Notes
50	20	F	Chond-P	2	84	28	R pat lat	300	ACI-C	09/11/01	58				
51	32	F	Chond-P	1	60	48	R pat multi	600	ACI-C	28/05/02	46				MACI vs ACI
52	32	M	Chond-P	4	24	66	R pat multi	1035	ACI-C	22/03/02	72				MACI vs ACI
53	45	F	Chond-P	1	72	51	R pat sing	875	ACI-C	07/11/00	10				
54	39	F	Chond-P	2	84	32	R pat sing	700	ACI-C	27/08/99	42	28			
55	30	M	Chond-P + trauma	5	36	23	R LFC	225	ACI-C + drilling to pat defect	05/05/00	42	96			
56	38	F	Chond-P	6	96	30	R pat multi	621	ACI-C	04/10/02	20				
57	54	F	Early OA	3	48	30	R troch	300	ACI-C	07/09/01	86	94			
58	31	F	OCD	2	156	22	L MFC	506.25	ACI-C	31/05/02	79				MACI vs ACI
59	18	M	OCD	1	48	52	LMFC	600	ACI-C	19/10/01	86				
60	43	F	OCD	1	36	58	L Pat multi	720	ACI-C	27/09/02	33				MACI vs ACI
61	34	M	OCD	2	240	23	L MFC	900	ACI-C	05/01/01	24				
62	38	M	OCD	2	144	42	L MFC	950	ACI-C	04/10/02	25				MACI vs ACI
63	44	F	OCD	3	18	32	L MFC	90	ACI-C	30/03/01	38	49			P vs C
64	26	F	OCD	1	180	40	L MFC	1125	ACI-C	16/03/01	70	71			P vs C
65	20	F	OCD	3	24	56	L MFC	225	ACI-C	21/09/01	91	100			P vs C

SPECIAL NOTE

THIS ITEM IS BOUND IN SUCH A MANNER AND WHILE EVERY EFFORT HAS BEEN MADE TO REPRODUCE THE CENTRES, FORCE WOULD RESULT IN DAMAGE

Pat no.	Age (yrs)	Sex	Cause	No. of operations	Dur. Of symp.	Cin Pre Op	Site	Size (mm^2)	Surg Proc	Date of 2nd stage	Cin 1 yr	Cin 2 yrs	Cin 3 yrs	Cin 4 yrs	Notes
66	22	F	OCD	1	156	40	L MFC	600	ACI-C	17/07/98	93	68	68		
67	43	M	OCD	1	120	47	L pat med	144	ACI-C	30/06/00	86	84	91		P vs C
68	25	M	OCD	2	72	58	R LFC	345	ACI-C	10/07/01	73				
69	15	M	OCD	1	24	68	R LFC	500	ACI-C	08/09/01	80				
70	22	M	OCD	2	30	77	R LFC	500	ACI-C	12/11/99	88				
71	18	F	OCD	1	72	62	R LFC	160	ACI-C	30/03/01	92	93			P vs C
72	36	F	OCD	2	276	13	R MFC	180	ACI-C	14/07/00	10	8	8		P vs C
73	21	M	OCD	2	36	26	R MFC	600	ACI-C	19/02/99	48	68	89	54	
74	16	M	OCD	1	60	56	R MFC	375	ACI-C	17/08/01	81	97			P vs C
75	26	M	OCD	1	228	58	R MFC	165	ACI-C	03/10/00	87				
76	25	F	OCD	1	72	50	R pat multi	525	ACI-C	05/02/99	89	91	54	75	
77	35	M	OCD	2	228	50	L MFC	1225	ACI-C	09/08/01	56				
78	39	M	OCD	2	60	24	L MFC	800	ACI-C	07/06/02	38				MACI vs ACI
79	43	M	OCD	3	96	43	R MFC	200	ACI-C	25/01/01	22				
80	25	F	OCD	1	156	73	R MFC	600	ACI-C	19/02/99	98	87	54	54	
81	30	M	OCD	4	156	32	R MFC	1200	ACI-C	31/08/01	38				
82	40	M	Other	4	96	30	L MFC	500	ACI-C	16/04/99	45	64	22	22	P vs C
83	30	F	Other	1	36	43	L MFC	600	ACI-C	12/03/02	50				MACI vs ACI
84	20	M	Other	1	24	43	L MFC	500	ACI-C	24/03/00	75	87			P vs C
85	18	M	Other	2	60	38	L MFC	500	ACI-C	02/08/02	76				
86	32	M	Other	3	276	14	L pat	204	ACI-C	16/04/99	64	71	52		
87	47	F	Other	1	36	42	L pat	400	ACI-C	02/02/01	88	80			
88	28	M	Other	1	84	41	L supra troch		ACI-C	09/03/01	92	98			
89	35	M	Other	2	48	32	R LFC	400	ACI-C	19/03/99	75	75	76	50	P vs C

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Pat no.	Age (yrs)	Sex	Cause	No. of operations	Dur. Of symp.	Cin Pre Op	Site	Size (mm^2)	Surg Proc	Date of 2nd stage	Cin 1 yr	Cin 2 yrs	Cin 3 yrs	Cin 4 yrs	Notes
90	31	F	Other		216	38	R LFC	150	ACI-C	13/04/99	79	68	87	60	
91	36	F	Other	1	18	29	R MFC	300	ACI-C	02/03/00	40	30	30		P vs C
92	31	M	Other	1	84	59	R MFC	375	ACI-C	10/05/02	43				MACI vs ACI
93	33	M	Other	1	156	26	R MFC	300	ACI-C	02/11/01	50				
94	46	F	Other	1	36	44	R MFC	280	ACI-C	18/01/00	73	93	94		P vs C
95	35	M	Other	2	96	60	R MFC	437.5	ACI-C	14/11/00	76	63			P vs C
96	37	M	Other	1	24	30	R troch	450	ACI-C	16/04/02	82				MACI vs ACI
97	39	M	Other + failed mosaic plasty	6	300	48	R MFC	625	ACI-C	25/06/02	26				MACI vs ACI
98	37	M	Other + previous failed MSP and mosaic plasty	5	168	20	L MFC	396	ACI-C	05/03/02	20				MACI vs ACI
99	19	M	Trauma	2	36	32	L LFC	600	ACI-C	18/12/98	38	42	24	30	
100	34	M	Trauma	2	18	70	L LFC	375	ACI-C	10/03/00	86	86	65		P vs C
101	36	F	Trauma	2	24	32	L LFC	218.75	ACI-C	09/03/99	88	87	58	65	
102	32	F	Trauma	1	36	32	L MFC	120	ACI-C	27/04/01	24	24			P vs C
103	37	M	Trauma	3	12	48	L MFC	225	ACI-C	09/07/98	25	42	46	66	
104	31	M	Trauma	1	36	69	L MFC	1250	ACI-C	18/12/01	52				
105	27	M	Trauma	2	18	43	L MFC	600	ACI-C	10/11/98	53				
106	33	M	Trauma	4	192	73	L MFC	660	ACI-C	05/01/01	57	57			P vs C

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107	46	M	Trauma	3	72	22	L MFC	450	ACI-C	31/05/02	58				MACI vs ACI
108	39	M	Trauma	1	36	66	L MFC	600	ACI-C	21/12/01	60	26			
109	34	M	Trauma	1	36	62	L MFC	156	ACI-C	22/02/02	62				
110	45	F	Trauma	2	180	44	L MFC	150	ACI-C + ACL recon	22/03/02	68				MACI vs ACI, comb
111	17	F	Trauma	1	48	29	L MFC	225	ACI-C	01/06/99	70	59			P vs C
112	43	F	Trauma	6	288	18	L MFC + troch	300	ACI-C + drilling troch	26/07/02	18				MACI vs ACI
113	33	F	Trauma	1	48	44	L pat	150	ACI-C	16/04/99	76	88	89	70	P vs C
114	49	F	Trauma	5	132	22	L pat med	450	ACI-C	15/06/01	46	38			
115	32	F	Trauma	1	108	36	L pat med	720	ACI-C	04/12/01	64				
116	34	F	Trauma	3	24	54	L pat med	195	ACI-C	01/06/99	89	75	54		P vs C
117	16	F	Trauma	2	84	22	L pat multi	300	ACI + Lat rel + med parapatela reefing	27/07/01	38	42			
118	34	F	Trauma	1	120	30	L pat multi	1050	ACI-C	16/02/01	64	36			

Pat no.	Age (yrs)	Sex	Cause	No. of operations	Dur. Of symp.	Cin Pre Op	Site	Size (mm^2)	Surg Proc	Date of 2nd stage	Cin 1 yr	Cin 2 yrs	Cin 3 yrs	Cin 4 yrs	Notes
119	27	F	Trauma	4	24	62	L pat sing	500	ACI + mosaic plasty lat edge of trochlea + drilling to harvest site + pat re-alignment	12/11/99	84	84	84	83	
120	38	F	Trauma	5	300	22	R LFC	195	ACI-C	10/05/02	20				MACI vs ACI
121	26	M	Trauma	3	120	36	R LFC	50	ACI-C	16/02/01	32	26			P vs C
122	38	M	Trauma	1		54	R LFC	288	ACI-C	13/09/02	63				MACI vs ACI
123	34	F	Trauma	1	36	15	R LFC	1200	ACI-C	24/11/00	67	67	76		P vs C
124	15	M	Trauma	2	12	58	R LFC	1000	ACI-C + osteotomy 6/12 later	19/04/02	78				comb
125	49	M	Trauma	1	20	58	R LFC	345	ACI-C	22/06/99	87	87	88	88	P vs C
126	16	M	Trauma	2	17	46	R LFC	300	ACI-C	25/05/01	96	100			P vs C
127	41	F	Trauma	1	54	30	R MFC	200	ACI-C	05/03/02	10				MACI vs ACI
128	30	F	Trauma	3	36	24	R MFC	500	ACI-C	04/09/01	32	24			P vs C
129	26	F	Trauma	3	12	15	R MFC	220	ACI-C	26/01/01	58	88	84		
130	34	M	Trauma	1	14	54	R MFC	360	ACI-C	05/10/99	84	74	79		P vs C
131	39	F	Trauma	2	24	62	R MFC	200	ACI-C	13/04/99	84	72	68	86	P vs C
132	34	M	Trauma	1	252	50	R MFC	900	ACI-C	21/11/00	88	86			Pvs C
133	18	M	Trauma	2	48	80	R MFC	400	ACI-C	26/11/99	96	69	100		P vs C

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134	15	M	Trauma	1	36	53	R pat lat	500	ACI-C	07/11/00	95	100			
135	20	M	Trauma	1	36	54	R pat med	1200	ACI-C	27/07/01	71	28			
136	47	M	Trauma	1	12	45	R pat med	280	ACI-C	01/03/02	72				MACI vs ACI
137	24	M	Trauma	2	24	44	R troch	200	ACI-C + drilling of defect over MFC	11/04/00	75	84	68		
138	38	M	Trauma	3	180	73	R troch	400	ACI-C	25/02/00	77	87	62		P vs C
139	34	M	Trauma	5	36	17	R troch	1050	ACI-C	02/06/00	78	44	46		P vs C
140	18	M	Trauma	1	36	46	R troch	500	ACI-C	17/02/99	89	92	94		
141	36	M	Trauma + failed ACI	3	60	54	L pat med	300	ACI-C	01/03/02	30				MACI vs ACI
142	31	M	Trauma + failed ACI	5	132	18	R MFC	224	ACI-C	26/07/01	22				
143	48	F	Trauma + failed ACI	2	180	24	L MFC	900	ACI-C	01/11/02	64				MACI vs ACI
144	29	F	Trauma + failed MSP	4	108	26	R MFC	600	ACI-C	20/06/00	50				
145	36	M	Trauma + failed MSP	4	120	16	R MFC	700	ACI-C	10/03/00	89				
146	30	F	Trauma + failed MSP	2	120	24	R pat med	875	ACI-C	10/03/00	68				

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147	28	F	Trauma + failed MSP	2	60	42	L pat multi	800	ACI-C	27/04/01	50				
148	28	F	Trauma + failed MSP	5	84	34	L MFC	525	ACI-C + ACL recon	28/05/02	42				MACI vs ACI, comb
149	21	M	Trauma +prev ACI to L LFC	4	60	42	L pat multi	600	ACI-C	01/12/00	24	30			
150	38	F	Trauma	3	36	30	R LFC	600	ACI-C	20/07/01	86	84			
151	46	F	Other	1	66	18	R MFC + R pat multi	400 600	ACI-C	20/11/01	12				
152	38	M	Trauma + previous failed MSP to L pat (1995)	3	288	14	L pat lat + L pat med	300 440	ACI-C	07/09/01	18				
153	28	M	Trauma	3	108	31	R Troch + R MFC	400 150	ACI-C + mosaic plasty to supralat troch ridge	26/03/99	31	17	18		
154	41	F	Other	2	36	36	R MFC + R pat multi	375 700	ACI-C	11/12/01	36				

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155	42	M	Trauma	1	60	63	L MFC + L pat lat	300 250	ACI-C	14/12/01	40				
156	38	M	Trauma	3	132	56	R pat multi + R troch	1250 300	ACI-C	21/12/01	52				
157	29	M	Trauma	1	12	24	L pat med + L LFC	500 1200	ACI-C	03/08/01	56	52			
158	48	M	Trauma	2	24	66	L MFC + L troch	100 225	ACI-C	05/02/99	96	78	78	84	
159	14	M	Other	2	24	62	R pat multi + R MFC	1000 1200	ACI-C	15/09/00	82	87			
160	48	M	Trauma	1	180	79	R MFC + R troch	500 75	ACI-C	02/03/99	84	77			
161	37	M	Trauma	3	96	61	L Troch + L pat lat	500 160	ACI-C	27/11/01	76				
162	38	M	Trauma	5	36	30	L pat med + L pat lat	500 300	ACI-C	24/11/00	62	40			
163	43	F	Other	1	18	37	R pat + R MFC	500 75	ACI-C	12/09/00	60	58			
164	52	M	Trauma	2	324	72	R pat multi	989	ACI-C	01/02/02	82				MACI vs ACI
165	34	M	Trauma	2	36	65	L MFC	600	MACI	17/10/03	83				
166	40	F	Trauma	5	120	50	R MFC	225	MACI	23/09/03	56				
167	34	M	Trauma	6	108	74	R MFC	300	MACI	18/09/03	26				

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168	37	F	Trauma	1	24	61	L MFC	400	MACI	25/07/03	82				
169	42	M	Trauma	2	72	67	R pat multi + R Troch	300 225	MACI	24/06/03	70				
170	40	M	Trauma	3	192	66	L MFC	400	MACI	22/05/03	72				
171	37	F	Trauma	2	18	51	L MFC	300	MACI + ACL	13/05/03	61				
172	46	M	Trauma	1	30	68	L MFC	500	MACI	09/05/03	56				
173	33	F	Trauma	2	204	20	L Pat multi	500	MACI	08/05/03	32				
174	35	M	Chond pat	3	36	40	R Pat multi	375	MACI	06/05/03	80				
175	45	F	OCD	1	17	38	L MFC	875	MACI	26/04/03	48				
176	50	F	Trauma	1	24	34	R Pat sing	200	MACI	15/04/03	55				
177	21	F	Chond pat	3	60	42	R Pat + R Troch	100 100	MACI	28/03/03	70				
178	42	M	Trauma	1	24	35	R MFC	750	MACI	28/03/03	82				
179	26	F	Trauma	4	192	26	R Pat med	300	MACI	21/03/03	60				
180	34	F	Trauma	3	120	36	R MFC	320	MACI	14/03/03	66				
181	47	M	Trauma	2	12	62	R MFC	630	MACI	01/03/03	96				
182	44	F	Chond pat	1	17	42	R Pat med	200	MACI	01/03/03	73				
183	19	M	Trauma	1	36	74	R Pat med	400	MACI	28/02/03	98				
184	47	M	Trauma	1	42	56	R MFC	50	MACI	26/02/03	60				
185	21	M	Trauma	9	72	67	R MFC + LFC	1575 700	MACI	26/02/03	81				
186	17	M	Trauma	1	36	58	L Pat sing	750	MACI	25/02/03	76				
187	37	M	Trauma	1	120	64	L MFC	630	MACI	14/02/03	54				

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188	31	F	Trauma	2	132	50	L MFC	450	MACI	13/02/03	30				
189	30	M	Trauma	2	168	28	L MFC	450	MACI	11/02/03	68				
190	23	M	Trauma	1	48	58	L MFC	200	MACI	06/02/03	30				
191	38	M	Other	1	456	68	L MFC	525	MACI	22/01/03	96				
192	21	F	Chond pat	2	120	56	L Pat multi	700	MACI	17/01/03	58				
193	28	M	Trauma	2	11	50	R LFC	875	MACI	10/01/03	84				
194	22	F	OCD	4	120	52	R MFC	875	MACI	20/12/02	77				
195	30	M	Chond pat	4	54	60	L LFC	700	MACI	20/12/02	97				
196	35	F	Trauma	3	24	22	L MFC	450	MACI	17/12/02	70				
197	33	M	Trauma	2	240	32	R Troch	750	MACI	11/12/02	83				
198	36	M	OCD	1	108	88	L MFC	320	MACI	03/12/02	94				
199	38	F	Other	2	60	30	R MFC	96	MACI	29/11/02	83				
200	37	F	Trauma	1	72	36	L MFC	600	MACI	22/11/02	50				
201	27	M	Other	1	156	42	L MFC	875	MACI	22/11/02	55				
202	33	M	Trauma	2	24	44	R MFC *2	500 48	MACI	29/10/02	57				MACI vs ACI
203	26	F	Other	1	9	46	L MFC * 2	500 10	MACI	29/10/02	69				
204	38	M	Early OA	1	456	62	L LFC	300	MACI + micro# tib plateau	29/10/02	80				MACI vs ACI
205	41	M	Trauma	1	48	66	L MFC	750	MACI + HTO	17/10/02	63				comb
206	30	F	Trauma	1	144	34	L MFC	375	MACI	08/10/02	12				MACI vs ACI
207	29	M	Trauma	1	24	40	R Pat multi	375	MACI	07/09/02	72				MACI vs ACI

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208	35	M	Trauma	2	60	30	R MFC	100	MACI + ACL recon	30/08/02	34				MACI vs ACI
209	26	F	Chond pat	5	108	36	L Pat multi	525	MACI	16/08/02	64				MACI vs ACI
210	42	F	Other	1	48	48	R pat lat	350	MACI	13/08/02	76				MACI vs ACI
211	19	F	Chond pat	2	54	29	R MFC	375	MACI	13/08/02	65				
212	23	M	Chond pat	1	72	50	R MFC	484	MACI sandwich	06/08/02	75				MACI vs ACI, comb
213	32	M	Chond pat	7	60	28	R Pat med	528	MACI	02/08/02	38				
214	45	F	Chond pat	1	60	51	R Pat multi	875	MACI	20/06/02	46				
215	43	M	Trauma	3	36	32	L MFC	300	MACI	18/06/02	12				MACI vs ACI
216	38	M	Trauma	1	156	57	L Pat med + L Troch	330 216	MACI	11/06/02	52				MACI vs ACI
217	46	F	Chond pat	2	66	40	R Pat med	220	MACI	31/05/02	26				MACI vs ACI
218	32	M	Trauma	3	150	45	L MFC	200	MACI + ACL recon	24/05/02	74				MACI vs ACI, comb

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219	21	M	Trauma	1	48	41	L MFC	250	MACI + ACL recon	14/05/02	95				MACI vs ACI, comb
220	44	M	Other	4	54	42	L LFC	750	MACI	03/05/02	81				MACI vs ACI
221	31	M	Trauma	4	156	56	L MFC	600	MACI + ACL recon	22/04/02	56				MACI vs ACI, comb
222	22	F	Trauma	7	48	62	L Pat lat + med, L Troch * 3	1200 150 600 750 150	MACI	17/04/02	85				MACI vs ACI
223	21	M	Chond pat	2	42	27	L Pat lat	500	MACI	16/04/02	52				MACI vs ACI
224	20	M	OCD	1	36	70	L MFC	800	MACI sandwich	16/04/02	96				MACI vs ACI, comb
225	41	M	Trauma	2	84	42	R Pat multi	375	MACI	12/04/02	14				MACI vs ACI
226	25	F	Other + failed MSP at 4 years	3	108	14	L Pat med	224	MACI sandwich	12/04/02	82				MACI vs ACI, comb

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227	34	M	Trauma + failed Mosaic plasty to MFC	4	60	44	R MFC	540	MACI	22/03/02	46				
228	27	F	Chond pat	2	180	34	R Pat multi	300	MACI	19/03/02	90				
229	30	F	Other	2	42	41	R MFC	300	MACI	15/03/02	62				MACI vs ACI
230	44	F	Chond pat	2	96	43	R Pat sing	645	MACI	15/03/02	42				MACI vs ACI
231	31	F	Chond pat	1	48	70	R Pat	300	MACI	08/03/02	68				
232	46	F	Chond pat	2	336	40	L MFC	600	MACI + bone graft	05/03/02	52				MACI vs ACI, comb
233	43	F	Trauma	1	24	46	R Pat lat + Troch	625 300	MACI	01/03/02	66				MACI vs ACI
234	21	M	OCD	2	36	43	L LFC	875	MACI	02/10/02	81				
235	73	F	Other	1	24	20	R Pat	400	MACI	13/02/02	72				
236	32	F	Trauma	2	24	29	L Pat	600	MACI	25/03/02	50				
237	20	M	Other	1	36	51	L Pat	360	MACI	27/03/02	90				
238	51	F	Other	2	12	73	L MFC	375	MACI	27/03/02	89				
239	25	F	Trauma	1	36	32	L Pat	400	MACI	13/05/02	64				
240	24	M	Trauma	1	9	40	L LFC	600	MACI	24/06/02	87				
241	40	F	Trauma	1	24	18	R Pat	150	MACI	18/07/02	22				
242	40	M	Trauma	2	40	52	L Troch	300	MACI	18/07/02	63				

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243	35	F	Other	2	36	36	R Pat + LFC	400 7	MACI	07/12/02	53				
244	45	M	Trauma	3	30	35	L Pat	700	MACI	18/01/03	84				
245	28	M	Other	1	24	62	R LFC	750	MACI	07/12/02	74				
246	34	M	Trauma	3	36	4	R LFC	200	MACI	05/02/03	68				
247	37	F	Trauma	1	16	63	L MFC	50	MACI	17/04/02	42				
248	36	M	Trauma	3	28	26	R MFC	800	MACI	27/05/02	32				
249	36	M	Other	1	36	62	R MFC	450	MACI	29/05/02	80				
250	31	M	Trauma	2	48	43	R MFC	200	MACI	24/06/02	87				
251	24	F	OCD	2	36	16	L MFC	400	MACI	12/08/02	36				
252	38	M	Trauma	1	24	30	L MFC	60	MACI	04/09/02	44				
253	50	M	Trauma	1	36	59	R MFC	400	MACI	21/09/02	38				
254	42	M	Trauma	2	30	50	R MFC	300	MACI	23/09/02	29				
255	33	M	Trauma	1	16	46	R MFC	150	MACI	28/09/02	44				
256	40	F	Trauma	1	18	44	L MFC	500	MACI	28/09/02	60				
257	38	M	Other	2	24	62	L MFC	150	MACI	30/09/02	90				
258	36	F	Other	3	60	58	R Pat	400	MACI	23/11/02	72				
259	39	F	Trauma	1	36	46	L Pat	225	MACI	27/11/02	72				
260	37	F	Other	0	24	20	L MFC	112.5	MACI	01/10/02	77				
261	51	M	Other	1	18	24	R MFC	120	MACI	26/02/03	44				
262	63	M	Trauma	3	60	38	L LFC	375	MACI	29/03/03	78				
263	26	M	Trauma	3	108	44	L LFC	900	MACI	28/05/03	72				
264	35	M	Trauma	1	20	58	R MFC	200	MACI	10/05/03	84				
265	29	M	Trauma	4	120	69	R Pat	144	MACI	31/05/03	82				
266	38	M	Other	2	36	22	R LFC	300	MACI	07/06/03	56				
267	40	M	Trauma	4	108	26	R MFC	450	MACI	09/06/03	53				
268	28	M	Trauma	3	30	47	R LFC	200	MACI	04/06/03	48				
269	39	M	Other	2	36	65	R MFC	1000	MACI	07/06/03	72				
270	46	M	Trauma	2	36	33	R MFC	400	MACI	09/07/03	32				
271	36	M	Trauma	5	54	16	L Troch + MFC	600 1200	MACI	06/08/03	62				

SPECIAL NOTE

THIS ITEM IS BOUND IN SUCH A MANNER AND WHILE EVERY EFFORT HAS BEEN MADE TO REPRODUCE THE CENTRES, FORCE WOULD RESULT IN DAMAGE

Pat no.	Age (yrs)	Sex	Cause	No. of operations	Dur. Of symp.	Cin Pre Op	Site	Size (mm^2)	Surg Proc	Date of 2nd stage	Cin 1 yr	Cin 2 yrs	Cin 3 yrs	Cln 4 yrs	Notes
272	28	M	Trauma	1	12	40	L pat multi	500	MACI	02/11/02	87				MACI vs ACI
273	20	M	Other	4	97	22	L pat lat	1600	MACI	18/06/02	22				MACI vs ACI

Abbreviations:

Cin: Cincinnati score.
Surg Proc: Surgical procedure.
OCD: Osteochondritis Dissecans.
Chond pat: Chondromalacia Patellae.
MSP: Matrix Support Prosthesis.
HTO: High Tibial Osteotomy.
Micro#: Microfracture
P vs C: Patients recruited for the prospective, randomised study comparing two techniques of Autologous Chondrocyte implantation for osteochondral defects in the knee: Periosteum covered versus type I/III collagen covered.
MACI vs ACI: Patients recruited for the prospective, randomised study comparing two techniques of Autologous Chondrocyte implantation for osteochondral defects in the knee: MACI vs ACI.
comb: Patients reviewed who had Chondrocyte implantation in the knee combined with other surgical procedures.